Opportunistic Infections and Mortality: Still Room for Improvement

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(See the major article by Djawe et al on pages 1366–75.)

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Among the accomplishments having the greatest impact during the first decade of the AIDS epidemic was the rapid development of effective tools and strategies to diagnose, treat, and prevent opportunistic infections. Prior to 1981, clinicians had little experience with managing infections such as pneumocystis pneumonia, *Toxoplasma cerebritis*, cytomegalovirus (CMV) retinitis, disseminated *Mycobacterium avium* complex infection, and chronic diarrhea due to cryptosporidia or microsporidia. Highly effective drugs to treat CMV and *M. avium* complex infection had not been developed for clinical practice, and many physicians used intravenous pentamidine, a relatively toxic drug, to treat pneumocystis pneumonia. Aided by randomized prospective clinical trials and the development of national guidelines to rapidly disseminate new information [1], clinicians quickly learned how to recognize and treat these syndromes and diseases.

In the eras when no antiretroviral therapy (ART) was available or when

ART was limited to single or dual nucleoside agents, median survival times after the diagnosis of the first AIDS-associated opportunistic infection were very limited, ranging from 2 to 22 months, depending on the infection [2]. Human immunodeficiency virus (HIV) testing was not widely available, and most patients presented to healthcare providers with an opportunistic infection. Accordingly, most patients had profoundly depressed CD4⁺ T-cell counts at the time of presentation. There were limited programs to support retention in care for HIV-infected patients and no effective treatments for restoring immunologic function.

In the late 1990s, with the development and availability of more-effective ART, immunity could be more effectively and durably restored, and health outcomes improved dramatically. To supplement the Ryan White Act of 1990 [3], more federal and local programs were developed to support retention in care. The management of opportunistic infections was improved by developing new molecular diagnostic tests, by developing new drugs, and by completing well-designed prospective studies. Medical support improved, especially in critical care departments where ventilator management, treatment for septic shock, and management of intracranial pressure, for instance, saw major advances [4, 5].

As a result of these developments, and with more-widespread use of ART, the incidence of HIV-related opportunistic infections began an impressive decline [6–8]. In this issue of the *Journal*, Djawe et al report data on mortality among 20 858 patients in San Francisco following diagnosis of their first AIDS-defining opportunistic infection, between 1981 and 2012. Data were considered in one of 3 eras: the pre-ART era (1981–1986), the era of mono- and dual-nucleoside therapies (1987–1996), and the era of highly active ART (1996–2012). San Francisco has one of the few health departments that have collected data continuously throughout the epidemic on initial and subsequent AIDS-defining opportunistic infections. The San Francisco Department of Health collects data by reviewing medical records at the time of diagnosis, as well as every 18–24 months thereafter. These data are collected on a citywide basis, rather than for select institutions or for highly specific cohorts. For 30 years, their data have supplemented cohort data and randomized trial data provided by other entities.

Not surprisingly, the authors found that survival following AIDS-defining opportunistic infections has improved markedly. The overall 5-year survival probability after the first opportunistic infection diagnosis was 7% in the pre-ART era, rose to 18% in the mono- and dual-nucleoside ART era, and reached

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65% in the highly active ART era. Survival improved dramatically for some opportunistic infections, such as pneumocystis pneumonia, Kaposi sarcoma, disseminated *M. avium* complex infection, and even immunoblastic lymphoma. For several opportunistic processes, however, such as central nervous system lymphoma and JC virus encephalitis, survival remains especially poor. These data are in line with reports from other cohorts and jurisdictions [9–13].

How satisfied should we be that morbidity and mortality resulting from HIV-related opportunistic infections are under control in the United States? In the current era, healthcare professionals and patients read projections that HIV-infected patients in the United States have the potential to live as long as their HIV-uninfected counterparts if durable HIV suppression is achieved [14]. These projections are encouraging for patients who have the social and economic resources to access medical care consistently. It is also encouraging that this report from Djawe et al supports the concept that such patients who are retained in care rarely develop opportunistic infections in the United States, if they receive their diagnosis relatively early (eg, when their CD4⁺ T-cell counts are >350 cells/mm³) and if they promptly achieve durable suppression of their HIV load.

Unfortunately, however, many geographic areas perform poorly with regards to achieving high rates of durable viral suppression in their HIV-infected populations [15, 16]. The importance of the so-called cascade of care, comprising early HIV diagnosis, effective linkage to care, long-term retention in care, and durable viral suppression, has long been recognized as being critical to attaining control over various aspects of the epidemic, including achieving good clinical outcomes in infected individuals. These data from San Francisco emphasize the importance of early HIV diagnosis, specifically before the CD4⁺ T-cell count becomes very low, and the importance of retention in care and receipt of appropriate

opportunistic infection prophylaxis and ART.

San Francisco may be a best-case scenario for reducing mortality risk associated with AIDS-related opportunistic infections. San Francisco has an enviable history of developing one of the earliest and most effective community responses to the HIV/AIDS epidemic and of developing a community of healthcare providers who are very well informed about HIV/AIDS. Additionally, during the first 2 decades of the epidemic, the affected population was a relatively homogenous, well-organized population of high-risk persons. However, even with >30 years of effort and engagement of all relevant stakeholders in San Francisco, the current report illustrates that HIV-related opportunistic infections continue to occur and that patients still die at alarming rates during the early years after their first AIDS-related opportunistic infection is recognized, as indicated in Figures 1 and 2 of the report. A 35% mortality rate within 5 years of diagnosis of the initial AIDS-defining opportunistic infection leaves considerable room for improvement.

Other areas in the United States face even more challenges than San Francisco. HIV has spread epidemiologically from the largest cities on the east coast and west coast to smaller cities, the Midwest and South, and rural areas. Those more recently affected regions often must deal with less experienced providers and more heterogeneous populations of patients developing HIV/AIDS, much like San Francisco has been grappling with more recently. Many of these jurisdictions lack the resources for extensive roll out of HIV testing, for getting HIV-infected patients into effective care early in the course of their disease, and for maintaining connection to care.

What are the lessons learned from this report from San Francisco and from the experience with opportunistic infections in other geographic areas? For patients in whom we failed to prevent HIV infection, we must recognize infection early so that interventions occur when disease is

mild, and we must provide programs that maximize the likelihood of durable viral suppression. We need to measure the presence and effectiveness of our cascade of care for each jurisdiction and to develop programs to achieve higher rates of success. It is not surprising that the data in this report support prior studies indicating that patients who had not been prescribed pneumocystis pneumonia prophylaxis or ART had worse survival than those who had been prescribed such drugs.

We must continue to educate providers to make certain that they recognize HIV-related opportunistic infections and manage them appropriately. Far too often, patients with recognized or unrecognized HIV infection present with syndromes that an experienced provider would consider highly suspicious of an HIV-related opportunistic infection but for which the empirical response from a less experienced provider is focused exclusively on non-HIV-related pathogens. In addition, we need better strategies to manage AIDS-related complications, especially malignancies, and we also need to be cognizant of the need to continue to develop new antimicrobial approaches for opportunistic infections in case unanticipated antimicrobial resistance develops.

The results from San Francisco are encouraging but highlight the need to remain focused on the potential for opportunistic infections to cause devastating disease. We have made considerable progress since the early 1980s. However, provider education about opportunistic infections is still important if we are to reduce the burden of HIV infection for patients who receive their diagnosis either late in the course of their infection or who do not attain durable virologic suppression.

Notes

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