

Present Situation and Future Prospects of the Collaborative Studies in Uganda: Treatment of HIV/AIDS Associated Opportunistic Infections

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INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a retrovirus that preferentially infects CD4 lymphocytes and lead to profound deficit in cellular immunity. The present HIV epidemic in Uganda is as severe as anywhere in the world. Among the total population of twenty million people, approximately two hundred people are estimated to be infected with HIV-1. This disease is, therefore, seriously affecting the Ugandan society. Compromised immune system renders HIV-infected adults more susceptible to a wide variety of pathogens. The patients with AIDS in Uganda are highly associated with opportunistic infection such as tuberculosis (TB), cryptococcal meningitis and others.

We, the Department of Internal Medicine, exchanged the memorandum for the collaborative studies with Makerere University in 1991, because the Dean of the Faculty of Medicine, Makerere University in Uganda visited our institute in 1989 and strongly requested for cooperation on the HIV/AIDS related studies. We, therefore, started the collaborative studies on AIDS-related opportunistic infections from 1993.

The purpose of the collaborative studies is to support the diagnosis and treatment of HIV/AIDS associated opportunistic infections in Mulago Hospital, Makerere University. We have already developed three projects on major opportunistic infections among HIV-infected Ugandan adult. First, we developed a study for cryptococcal meningitis in AIDS patients. We, next, developed a study on the treatment of pulmonary tuberculosis in HIV-infected persons. Finally, we carried out a study on community-acquired pneumonia. We introduce the studies on cryptococcal meningitis and community-acquired pneumonia.

Diagnosis and treatment of cryptococcal meningitis in patients with AIDS in Uganda

Cryptococcal meningitis is the most common invasive fungal infection in patients with AIDS, occurring in up to 30% in sub-Saharan Africa. This disease is regarded as a life-threatening opportunistic infection particularly in Africa. Fluconazole, one of the recently developed triazole antifungal drugs, shows a promising effect in the treatment of cryptococcal meningitis in patients with AIDS. To establish the easily-managed and cost-effective an-

ticryptococcal therapy for AIDS-associated cryptococcal meningitis in developing countries, this study was designed to compare the effects of treatment with low-dose oral fluconazole and short-term flucytosine with that of fluconazole alone (1). This study was developed from January to December in 1994. HIV seropositive patients over 16 years old were enrolled, if they presented cryptococcal meningitis-like symptoms and positive for cryptococcal staining or antigen in cerebrospinal fluid.

30 of 58 patients were randomized to receive combination therapy, and 28 were randomized to receive fluconazole monotherapy. Before treatment, almost all of the patients had headache, described as severe by 91% of patients. Half of the patients showed decreased consciousness. With respect to opportunistic infections other than cryptococcal meningitis, oral candidiasis was most frequently observed in 69%, and pulmonary tuberculosis was diagnosed in 9%. The mean CD4 and CD8 peripheral blood counts were 77 and 208/mm³, respectively. There was no significant differences with respect to demographic characteristics, laboratory values, or clinical symptoms and sign between the treatment group at baseline.

We could evaluate the survival rate of 50 patients at the end point of primary therapy and maintenance therapy for six months (Figure 1). Ten out of 25 patients receiving the monotherapy with fluconazole died within two weeks after the initial therapy, and only nine

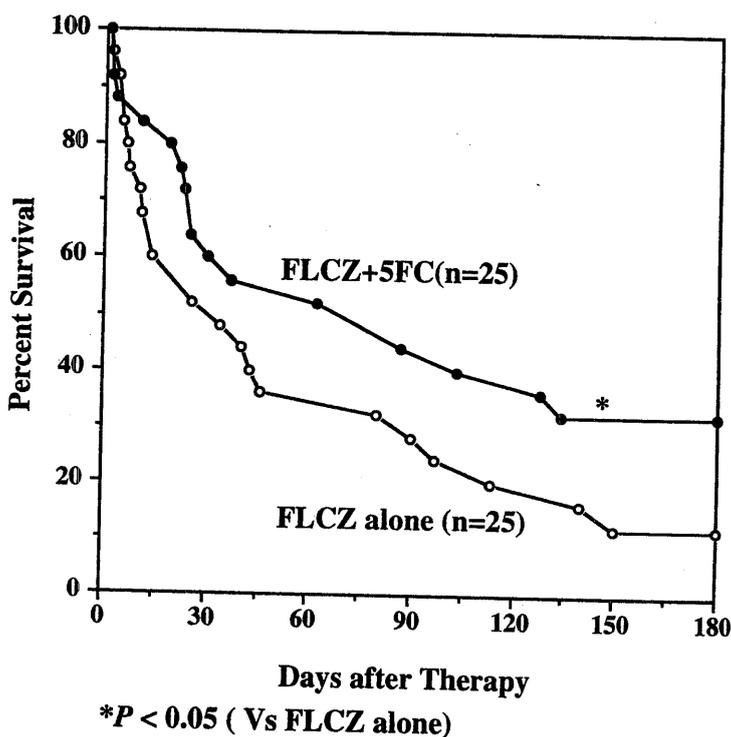


Figure 1. Survival of AIDS patients with cryptococcal meningitis during oral fluconazole with or without flucytosine in Uganda. FLCZ; fluconazole, 5FC; flucytosine.

of these patients (36%) survived for two months. In contrast, the combination therapy reduced the early deaths among these patients during the first two weeks, and 14 of 25 patients assigned to the combination therapy survived the full two months of initial therapy. At the end of the primary and maintenance therapy for 6 months, the survival rate of 25 patients receiving the combination therapy (32%) was significantly higher than that (12%) of the 25 patients assigned to the monotherapy. Despite the improved survival rate in patients receiving the combination therapy, the rate of positive cryptococcal cultures in cerebrospinal fluid remained high at 2 months and 6 months post-treatment, respectively. These data indicated that a large proportion of the patients had quiescent disease both at the end point of primary and maintenance therapy. No serious adverse effects were noted in any of the enrolled patients during the primary or maintenance therapy.

These data support that treatment with fluconazole is a cost-effective and safe regimen that improve the quality of life for patients with associated cryptococcal meningitis in HIV-epidemic developing countries. We, however, have the following problems. First, we still have a high mortality despite oral anti-cryptococcal drugs. Second, the total management of the treatment for cryptococcal meningitis in AIDS patients is difficult. Third, it is expensive to supply the adequate antifungal chemotherapy.

Diagnosis and treatment of community-acquired pneumonia among Ugandan adults

In tropical and developing countries at least one third of deaths are due to pulmonary infections. Before the outbreak of HIV infection in Africa, *Streptococcus pneumoniae* (*S. pneumoniae*) was reported to be only one predominant pathogen of acute pneumonia. However, clinical and microbiological characteristics for community-acquired pneumonia in HIV-seropositive patients in Africa have not fully investigated. In this study, we evaluated clinical and microbiological features, and clinical effectiveness by ampicillin therapy for community-acquired pneumonia among Ugandan adults particularly in the respect to HIV infection (2).

The study was done from 1996 to March 1998. Patients over 16 years old were enrolled if they were confirmed to have acute pneumonia by clinical symptoms and findings of chest radiograph. Quantitative culture method on rabbit blood agar and Gram's staining for freshly expectorated sputum was used for microbiological diagnosis.

More interestingly, 72.5% of 91 patients with community acquired pneumonia were infected with HIV-1. Their mean CD4 peripheral-blood counts and CD4/CD8 ratio were 330/ mm^3 and 0.48, and these were significantly lower than those in HIV-seronegative patients. For severity of community-acquired pneumonia, there was no difference in respiratory rates, pulse oxymetry oxygen saturation (SpO_2), extent of pneumonia on chest radiograph, and other inflammatory data between HIV-seropositive and HIV-seronegative patients at baseline.

Causative pathogens were determined by sputum or blood samples in 45 cases. Similar pattern of causative respiratory pathogens were identified in both groups, and major pathogens were *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Klebsiella pneumoniae*.

Parental ampicillin therapy followed by oral amoxicillin for one weeks was given immediately after enrollment. Clinical effectiveness was evaluated by improvement of clinical

symptoms and signs, and laboratory markers, and chest radiographs. We found 15 cases of fair and poor responders in HIV-seropositive individuals, while there was only one fair responder in HIV-seronegative individuals. More importantly, the mean CD4 peripheral blood cell counts in the fair and poor responders were lower than those in good responder in HIV-seropositive patients.

These data support that a large part of patients with community-acquired pneumonia in Uganda were infected with HIV-1. No difference of causative pathogens was noted between HIV-seropositive and HIV-seronegative patients. HIV-1 associated immune suppression appeared to decrease the clinical effectiveness of ampicillin therapy for community-acquired pneumonia. These data indicate that bacteriological diagnosis and careful antibiotic therapy are required for patients with community-acquired pneumonia.

Present situation of the collaborative studies

As introduced here, we have successfully carried out collaborative studies on treatment of HIV/AIDS related opportunistic infections during the last seven years. We feel that more training of physicians or technicians are necessary for the high quality studies. Although we obtained the meaningful results in our collaborative study, how the knowledges and experiences from these studies are utilized for the clinical practice in the study place?

Nevertheless, the published data may attract the attention for researchers or clinicians inside and outside of Uganda. These secondary benefits may increase global recognition of medical needs in specific area and may change the priorities of governmental agencies, as quoted in editorial response of a certain journal (1).

Future prospects of the collaborative studies

What is the future prospects and the goal of our collaborative studies? Not only to produce the data, but also to integrate the knowledge or technology into the training in special field of studies is important. Their knowledge and experiences could be utilized for future projects and clinical practice in Uganda. It is also possible to develop basic studies on infectious diseases in tropical area in certain research center in Uganda.

In summary, these processes of collaborative studies may produce fruitful results which contributes to the clinical practice in Uganda, and promote to obtain the government supports for specific infectious diseases.

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