

# Clinical Research, Prophylaxis, Therapy, and Care for HIV Disease in Africa

## ABSTRACT

By the end of the century, citizens of resource-poor countries will constitute 90% of the world's human immunodeficiency virus (HIV)-infected people. Clinical management of such persons in developing countries has been neglected; most AIDS research has concentrated on epidemiology, and donor agencies have generally invested in the prevention of HIV infection. The heavy burden of HIV disease in Africa requires that care for AIDS be addressed, and prevention and care should be seen as interrelated. Prevention and treatment of tuberculosis, the commonest severe infection in persons with AIDS in Africa, illustrate this interrelationship. We outline priorities for applied research on the management of HIV disease in a resource-poor environment, and discuss prophylaxis, therapy for opportunistic diseases, terminal care, and use of antiretroviral therapy. Research should define the standard of care that can realistically be demanded for HIV disease in a resource-poor environment. Research and public health programs for AIDS in developing countries must address AIDS care and attempt to reduce the widening gap between interventions available for HIV-infected persons in different parts of the world. (*Am J Public Health*. 1993;83:1385-1389)

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### Introduction

Clinical management of human immunodeficiency virus (HIV) disease in resource-poor countries has been a neglected subject. Yet the World Health Organization estimates that 13 million people worldwide have been infected with HIV types 1 and/or 2 since the beginning of the epidemic. With less than 10% of the world's population, Africa has more than 60% of the world's HIV-infected adults and more than 90% of the world's HIV-infected children. In South and Southeast Asia, more than 1 million persons are believed to have become infected since the mid-1980s.<sup>1</sup> By the end of the century, there will be a cumulative global total of 30 to 40 million HIV infections and of almost 10 million acquired immunodeficiency syndrome (AIDS) cases, 90% of which will be in citizens of the developing world.<sup>1</sup>

International efforts and donor agency funds for AIDS have been directed toward prevention and control programs in resource-poor countries.<sup>2</sup> Although understandable until now, however, this approach ignores the reality of increasing numbers of ill and dying people. Reluctance on the part of donors to deal with AIDS care is widening the divergence between the approach to AIDS in developing countries and that in industrialized ones, where there is increasing emphasis on secondary prevention and treatment for those already infected with HIV.

Providing care for the millions of people in developing countries who will become ill and die with AIDS in the 1990s will be one of the most difficult challenges posed by the pandemic in this last decade of the century.<sup>3-6</sup> In this paper we examine needs for responses beyond prevention and propose priorities for clinically oriented international AIDS research. Our discussion focuses on Africa because of our experience there, but many of the issues raised are relevant for other areas in the developing world.

### Clinical Care for HIV-Related Illness in Industrialized vs Developing Countries

Since early on in the epidemic, advances in the care of HIV infection and associated opportunistic diseases in industrialized countries have resulted in better survival and improved quality of life for patients with AIDS, and in delayed progression to AIDS in HIV-infected persons.<sup>7-10</sup> In addition to antiretroviral treatment, considerable experience has been gained in prophylaxis against certain diseases, including pneumocystosis and tuberculosis. Public health guidelines have been published concerning antiviral therapy<sup>11</sup> and prophylaxis for specific opportunistic infections,<sup>12-14</sup> leading to defined and accepted standards of practice. Great public health emphasis has been placed on secondary prevention, the needs of which have influenced even the surveillance case definition for AIDS.<sup>15</sup>(pp 4-19)

In developing countries, on the other hand, access to therapy for patients with HIV disease is extremely limited. Compared with the attention shown to other major causes of infectious morbidity and mortality, such as malaria, respiratory infections, and diarrhea, little attention has been given to defining standards of treatment for or case management of HIV-

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**TABLE 1—Rank Order of Causes of Death in Hospitalized HIV-Positive Adults Dying and Autopsied in Abidjan, Côte d'Ivoire**

Rank Order	Disease
1	Tuberculosis
2	Cerebral toxoplasmosis
3	Bacteremia
4	Bacterial pneumonia
5	Pyogenic meningitis
6	Wasting—no specific pathology
7	Other

infected individuals, or to evaluating treatment. Few data exist concerning the major causes of morbidity and mortality in African patients with HIV or the prevalence and time sequence of different opportunistic infections. Thus, the ability to prioritize diagnostic and treatment requirements has been limited. Use of antiretroviral drugs is exceptionally unusual because of cost, and prophylaxis against specific diseases is not routinely practiced. There has been little discussion of what kind of terminal care is required for patients dying of AIDS in developing countries. Some nongovernmental and church-based organizations have established pioneering programs and services providing community-level care for persons with AIDS and their families.<sup>16,17</sup> For the most part, however, AIDS care in the context of Africa's already frail health infrastructures is limited to symptomatic treatment, automedication, or no treatment at all.

A lack of resources for treating AIDS, the poor prognosis of AIDS patients, and the limited resources available for treating other diseases constitute the argument against more investment in AIDS care in developing countries. AIDS, however, is different from other medical diseases in its recent discovery, epidemiology, proportions, and implications. Its epidemiology and clinical presentation combine the features of an acute infection with those of a chronic disease, with large numbers of people affected. The impact of AIDS on Africa is similar to that of a natural or manmade disaster, and it carries with it the same requirement for intervention to improve survival and relieve widespread suffering.

Thus, although differences in access to life-prolonging therapies for other diseases in industrialized and developing countries are long-standing, they have

never been as large as they are in the case of AIDS. We may not be able to eliminate such differences, but simply to accept them is profoundly unjust. Moreover, addressing some of the international inequities concerning AIDS care could be the stimulus needed to deal with other inadequacies, such as the need for a global response to tuberculosis,<sup>18</sup> that should have been examined long ago.

### *The Interrelationship of Prevention and Care*

Inability to provide medical assistance for the complications of HIV infection undermines the credibility of prevention and control programs, and the interrelationship between and synergistic effect of care and prevention needs to be recognized. Interventions for sexually transmitted diseases and tuberculosis provide relevant examples. Both are closely linked to HIV infection: sexually transmitted diseases facilitate transmission and acquisition of HIV,<sup>19,20</sup> and tuberculosis (as well as some sexually transmitted diseases) acts as an opportunistic infection whose clinical picture may be modified by HIV.<sup>18,21</sup> Control of both requires access to treatment. Given the recently raised possibility that tuberculosis may modify the course of HIV infection,<sup>22</sup> treatment of tuberculosis may actually constitute secondary prevention for HIV disease.

Providing medical care for HIV-infected persons offers a unique opportunity to initiate prevention activities; at the moment of clinical consultation, health care workers can discuss contact tracing, provide vaccination for infants, prescribe prophylactic and/or curative therapy, undertake counseling and health education, and promote condom use. The experience of several grass-roots organizations in developing countries with high rates of HIV infection has been that behavioral change is enhanced by a supportive social and community environment, which includes respect, acceptance, and access to clinical care for those affected.

If quality of care improves, early diagnosis of HIV infection through wider access to voluntary HIV testing will further influence medical management, as happened for example, with the initiation of chemoprophylaxis for tuberculosis. Early diagnosis will also provide increased opportunities for counseling and public health education.

### *Staging of HIV Infection and Disease*

The staging of HIV infection,<sup>15(pp1-4)</sup> which is heavily dependent on CD4+ T-lymphocyte counts, plays a central role in therapeutic decision making for AIDS patients in industrialized countries. CD4+ T-lymphocyte counts are generally inaccessible in resource-poor countries, and there have been few attempts to design appropriate staging systems or to evaluate possible surrogate markers for these counts.

Studies in Abidjan have shown that only 10% of HIV-infected patients died with CD4+ T-lymphocyte counts above 200 mm<sup>3</sup>, which indicates that death is generally associated with quite advanced immunodeficiency (Projet RETRO-CI, unpublished observations). However, the limited data available also suggest that African patients with AIDS die at higher CD4+ T-lymphocyte counts than patients in industrialized countries, where death is now rare at CD4+ T-lymphocyte counts above 50 mm<sup>3</sup>.<sup>23</sup> These observations suggest that prophylactic treatment could prevent the onset of potentially fatal disease and that curative therapy for specific opportunistic infections could extend useful life.

Three broad categories of patients with HIV infection provide a framework for clinical management and definition of research priorities:

- Asymptomatic patients who have been diagnosed HIV positive early in infection. Such patients might benefit from prophylactic therapy aimed at specific diseases.
- Patients with early disease. Tuberculosis is likely to be the most frequent opportunistic disease, and many such patients will be treated in outpatient clinics. These patients require specific therapy but may also benefit from prophylaxis.
- Patients with end-stage disease. In this case, tuberculosis of the disseminated variety is the commonest pathology, but outcome despite treatment is poor.

### *Priorities for Clinical and Operational Research*

Table 1 shows the major clinical pathologies in dying, hospitalized HIV-positive adults in Abidjan, as determined by autopsy.<sup>24</sup> Three treatable diseases—tuberculosis, toxoplasmosis, and bacterial septicemia—caused 57% of all HIV-associated deaths; the first two conditions are

also preventable. Bacterial septicemia, especially with *Streptococcus pneumoniae* (in Kenya) and *Salmonella* (in Kenya and Côte d'Ivoire), has also been incriminated as a frequent cause of morbidity and mortality.<sup>25,26</sup>

Without specific knowledge of the major infections and causes of death in African patients with AIDS, treatment remains haphazard. Priorities for research on the management of AIDS in Africa are outlined in Appendix 1. A first research priority for different communities, then, is to determine what the most important HIV-associated opportunistic diseases are. It is likely that tuberculosis will dominate the list in the developing world. Local patterns may vary, however; cryptococcosis and Kaposi's sarcoma, for example, seem commoner in East than in West Africa. Such studies should combine in vivo investigation with postmortem pathology studies. Investigations of this kind have determined that certain opportunistic diseases such as *Pneumocystis carinii* pneumonia are uncommon and therefore should not be a priority for further prophylactic or therapeutic research.<sup>27</sup> However, if clinical care improves and survival increases, some previously unimportant diseases such as cytomegalovirus infection and lymphoma may become clinically relevant.

Combined with research into the relative frequency of opportunistic infections should be investigations of staging systems of HIV infection that can be used in the African context.<sup>28</sup> The use of total lymphocyte counts as surrogate markers for CD4+ T-lymphocyte counts requires evaluation in the developing country setting.<sup>29</sup>

A second research priority is to assess whether prophylactic measures can prevent the development of the common opportunistic infections such as tuberculosis or toxoplasmosis, and, if so, to determine when in the course of HIV infection such therapy should be used. These issues need to be addressed through controlled clinical trials. Whether such interventions improve survival and quality of life should also be assessed.<sup>30</sup>

A third priority is to evaluate standardized approaches to diagnosis and therapy for the common opportunistic infections. In the same way that simplified diagnostic approaches are being evaluated for sexually transmitted diseases, low-technology diagnosis of the common AIDS-associated infections needs to be developed, allowing for algorithmic treatment based on the recognition of syn-

dromes. Drug combinations should be as cost-effective as possible and standardized as recommended for the treatment of sexually transmitted diseases or tuberculosis. These diagnostic and therapeutic approaches require evaluation in controlled clinical trials.

The fourth priority for research should be to investigate ways of providing terminal care at an individual level as well as at the level of whole communities. Patients with end-stage HIV disease require care in the broadest sense of the term. We have surprisingly poor understanding of the common symptoms that cause suffering in African patients dying of AIDS. For example, although the HIV wasting syndrome has stimulated academic discussion about pathophysiology, we do not even know to what degree African patients are wasted because of inadequate food intake from painful esophagitis, weakness, or sheer poverty. More investigation is also needed into the physical, medical, and social needs of terminally ill AIDS patients; the requirements for drugs providing symptomatic relief; and the ways that care could be delivered. AIDS has turned medical wards in some African hospitals into places where the dying are abandoned, and use of community or hospice care for the increasing numbers of terminally ill persons should be investigated.

Finally, there is need for operational research to investigate how knowledge from the types of studies outlined above can be applied. Several groups have attempted to provide guidelines for the algorithmic treatment of HIV disease.<sup>7,31,32</sup> In addition, considerable experience exists with home care programs established by nongovernmental organizations in several African countries. Operational research must examine the feasibility of applying what has been learned on a large scale, including examination of the efficacy and application of algorithmic approaches, and of delivering chemoprophylaxis.

### *The Role of Antiviral Drugs*

The main limitations to the use of currently available antiviral drugs for HIV disease in resource-poor countries are their cost, their side effects, their limited efficacy, and the need for close medical supervision during therapy. In the long term, however, restricting the use of antiretroviral drugs to persons from the North while an increasing proportion of HIV-infected people are citizens of the re-

source-poor South should be considered unacceptable.

The development of antiretroviral drugs appropriate for use in developing countries should be a priority. This would also be relevant to industrialized countries, where access to antiretroviral therapy is also influenced by economic factors. Currently available drugs, such as zidovudine, should become more accessible to resource-poor countries even if their use will remain unequal. Antiretroviral therapies could conceivably be provided at reduced prices if demand for them in developing countries were substantially increased.

### *Community and Government Attitudes*

AIDS advocacy groups in industrialized countries have influenced ways in which drug trials are conducted and have increased access to care for their constituents.<sup>33</sup> In contrast, HIV-infected persons from developing countries are rarely heard. It is time that their opinions about issues concerning them are actively sought.

HIV/AIDS prevention and control programs need to develop and incorporate standard approaches to clinical care of HIV-infected persons. Donor agencies, ministries of health, and nongovernmental organizations should work together to provide cost-effective, quality treatment and care for HIV infection, as has happened to a great extent in many industrialized countries.

The expected outcome of better care must be realistic. Although HIV disease will remain fatal, the relief of suffering is a universal aim of health care. Short-term increases in survival and quality of life of HIV-infected adults at the height of their family and community responsibilities may significantly affect those around them, especially when large numbers are involved. The humanitarian imperative for care for AIDS patients in Africa challenges concepts of sustainability. Better coordination between donors and avoidance of duplication of effort will be essential for optimal use of resources.

### *Conclusions*

Care for persons with HIV disease in Africa has been inadequately addressed. We have attempted here to draw attention to this unmet need, to point out the divergent approaches to treating the AIDS ep-

idemic in the industrialized and developing worlds, and to propose potential areas for research and intervention. We are not arguing for all resources to go into care at the expense of prevention; we are arguing, however, for more funding for prevention, for adequate funds for care, and for recognition that prevention and care are interdependent.

In the same way that multicenter studies, such as the AIDS Clinical Trial Group and Concorde trials, have influenced AIDS care in the United States and Europe, such studies could also be organized in Africa to address the research needs for the therapeutic interventions outlined above. With the help of international agencies, a consortium involving universities, public health institutes, non-governmental organizations from industrialized countries and their counterparts, and ministries of health in developing countries could conduct the necessary multidisciplinary research.

If we do nothing to address the requirements for care as the epidemic in Africa progresses, we will be justifiably criticized for having shown great interest in the study of AIDS in Africa but little interest in Africans who have AIDS. □

## Acknowledgments

Pathology work at Projet RETRO-CI has been funded in part by the Global Programme on AIDS, World Health Organization, the Medical Research Council of the United Kingdom, and the Rockefeller Foundation.

We thank the many colleagues in Africa, Europe, and the United States with whom we have discussed priorities for AIDS research. The suggestion of a consortium of universities to work on different aspects of AIDS in Africa was first made by Dr J. B. McCormick. We thank colleagues at Projet RETRO-CI for their support, and clinical colleagues in Abidjan who have allowed us access to their services, especially Professors A. Yapi, B. Beda, N. Ezani, J.-M. Kanga, C. Giordano, N. Coulibaly, M. Honde, A. Dago Akribi, and Drs I.-M. and D. Coulibaly.

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**APPENDIX—Priorities for Research on the Management of AIDS in Africa****Study of HIV-associated opportunistic diseases**

- Determine the relative frequency of different opportunistic diseases in HIV-positive persons.
- Determine the relative order of appearance of opportunistic diseases in relation to increasing immunodeficiency.
- Determine the relative frequency of opportunistic diseases as causes of death in HIV-positive persons.
- Develop and evaluate widely a usable HIV staging system.

**Prophylaxis for specific opportunistic diseases**

- Assess chemoprophylactic regimens for specific opportunistic infections (tuberculosis, toxoplasmosis, etc.) in HIV-infected persons.

- Assess maintenance therapy in HIV-positive persons following specific infections (e.g., tuberculosis).

**Treatment algorithms**

- Develop and evaluate diagnostic and treatment algorithms for opportunistic diseases appropriate to the different levels of the health care system.

**Terminal care**

- Determine needs (medical, social, etc.) of terminally ill AIDS patients.
- Develop and evaluate algorithms for symptomatic treatment and terminal care.
- Evaluate hospital vs hospice vs community care of terminally ill AIDS patients.