

Review

HIV Pharmacotherapy Issues, Challenges, and Priorities in sub-Saharan African Countries

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The use of potent antiretroviral drugs has led to successful treatment of HIV infection in most high-income countries. However, therapy remains largely unaffordable to the resource-limited world, particularly to countries in sub-Saharan Africa. The disparity and subsequent disease burden are devastating to the poorly resourced countries, hence creating a greater demand for international collaboration. This review outlines key examples of emerging HIV pharmacotherapy issues, challenges, and priorities within resource-limited settings in order to lay groundwork for potential enhancement of international research collaboration efforts. The prevalence and distribution patterns of HIV infection and sociocultural factors found in sub-Saharan African settings are discussed. Challenges include drug financing, drug distribution infrastructure, and government commitment to responding to the HIV pandemic. Priorities include prevention of HIV transmission, management of pediatric patients, availability of affordable medicines, and addressing concerns over the quality of medicines. The potential for effective international collaboration is enhanced when expertise and resources from the developed world are combined with an understanding of the unique priorities of resource-limited settings.

Introduction

Since the recognition of AIDS in the early 1980s, standards of treatment and care have evolved considerably. However, a great disparity exists between the extent of pharmacotherapy advancement in wealthy versus poor countries. In most developed countries, research has led to the discovery of therapeutic agents that reduce morbidity and mortality associated with HIV by more than 80%.¹⁻³ In resource-limited countries AIDS continues to be the major cause of mortality. Of the estimated 40 million people living with HIV in December 2006, more than 95% were in resource-limited countries.⁴ More than 98% of deaths among adults and children from HIV or AIDS in 2006 were also from this setting.

The major challenge is translating and disseminating therapeutic advances in the developed world to the developing countries where the demand is greatest. Increased international collaboration has been called for as a method of addressing this question.⁵ However, collaboration does not simply consist of the implementation of experiences from the well-resourced settings. There are many epidemiologic, social, cultural, economic, political, and technologic differences that affect HIV and AIDS pharmacotherapy implementation in resource-limited settings. These need to be considered and addressed when designing relevant approaches to HIV and AIDS management in these countries.

The goal of this review is to provide some key examples of emerging HIV and AIDS pharmacotherapy issues, challenges, and priorities within resource-limited sub-Saharan African countries, and highlight how they contrast with those of the developed world. This review is intended to contribute to better understanding of the approaches needed in the developing countries and potentially lay the groundwork for improved international collaboration.

Issues that Impact HIV Pharmacotherapy Delivery

Prevalence and Distribution of HIV Infection

HIV infection rates are disproportionately higher in sub-Saharan African countries than in developed countries. Table 1 shows regional HIV statistics for the end of 2006 indicating an adult prevalence rate of 5.9% in sub-Saharan Africa. It has been estimated that there are 24.7 million HIV-seropositive adults and children in this region. Although the area consists of approximately 10% of the world's population, it accounts for 60% of all people living with HIV. In the same region in 2006 an estimated 2.8 million people acquired HIV infection and 2.1 million adults and children died of AIDS.⁴

Despite a high prevalence of HIV and AIDS in sub-Saharan Africa, national health programs in these resource-poor

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Table 1. Regional HIV and AIDS Statistics, December 2006

Region	HIV-seropositive Adults and Children	Adults and Children Newly Infected with HIV	Adult Prevalence Rate
Sub-Saharan Africa	24.7 million	2.8 million	5.9%
North Africa and the Middle East	460,000	68,000	0.2%
South and Southeast Asia	7.8 million	860,000	0.6%
East Asia and Pacific	750,000	100,000	0.1%
Latin America	1.7 million	140,000	0.5%
Caribbean	250,000	27,000	1.2%
Eastern Europe and Central Asia	1.7 million	270,000	0.9%
Western and Central Europe	740,000	22,000	0.3%
North America	1.4 million	43,000	0.8%
Total	39.5 million	4.3 million	1.0%

Adapted from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) AIDS Epidemic Update, December 2006.

countries cannot afford the essential medicines, especially antiretroviral therapy. The net effect is that while high-income countries now focus on improving the effectiveness of already established antiretroviral regimens, resource-limited countries are still struggling to make medicines widely accessible. According to the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS), at the end of June 2006, antiretroviral therapy coverage for sub-Saharan Africa was 23% of those deemed eligible for treatment by WHO/UNAIDS guidelines; the overall coverage for low- to middle-income countries was 24%.⁴

Faced with the overwhelming HIV and AIDS epidemic, sub-Saharan African countries with limited resources are managing the emergency using epidemiologic approaches as opposed to individualized patient therapy. Programs are more interested in regimens that can be used effectively and safely in the majority

of patients than in regimens that focus on catering to individual patient differences. There is also greater focus on prevention than treatment programs.⁶⁻⁹ As a result, the WHO has responded to this need by promoting the Essential Drugs Program in these countries.¹⁰

In 2006, of the more than 4 million people who were newly infected with HIV, 8% were children, approximately 90% of whom live in sub-Saharan African countries and were infected through mother-to-child transmission.⁴ Despite tremendous progress in preventing mother-to-child transmission of HIV, the high incidence of disease among children raises a number of other important issues, such as the availability of suitable pediatric drug formulations, adherence issues among pediatric populations, and the effect of nutritional status on therapeutic response. Such issues can have a profound impact on therapeutic priorities in these countries, as later discussed.

Sociocultural Factors

Stigma. Due to cultural factors and the culturally well-accepted stigma associated with HIV and AIDS, patients in sub-Saharan African countries tend to seek medical help only at advanced stages of disease. As a result, health care systems are forced to manage heavily ill patients.^{6,11} This poses an additional challenge in choosing therapeutic agents since research has suggested that heavily ill patients are more likely to suffer from adverse effects, in addition to finding it more difficult to take complicated regimens.

Socioeconomic Status. A good example of the role of socioeconomic status in HIV pharmacotherapy delivery is the debate over the use of protease inhibitors (PIs) in potent antiretroviral therapy for sub-Saharan African countries. In high-income countries, PIs are considered to be essential for the complete success of antiretroviral therapy, particularly in heavily ill patients with high viral loads.¹² However, these drugs are more expensive than other antiretroviral medications, generally require more frequent dosing, and are associated with more drug interactions, making them less favorable in the sub-Saharan African countries even though they have become part of the standard of care in other countries.

Traditional Beliefs. Sub-Saharan Africa is endowed with traditional and religious beliefs that may discourage the use of modern health facilities in these countries.¹³ Additionally, the medicines used for HIV and AIDS treatment according to certain traditional and religious beliefs may interact with antiretroviral therapy. Two commonly used South African herbal medicines from the plants *Hypoxis hemerocallidea* (African potato) and *Sunderlandia* have been shown to inhibit CYP3A4 activity by 34% to 87% and 64% to 96%, respectively, when their water and methanol extracts tested at concentrations of 100 mg/mL.¹⁴ This suggests a potential for clinically significant interactions with antiretroviral drugs, particularly PIs.

This situation is further complicated when the active ingredients in these traditional medicines are unknown and when they are not used in consistent dosages. Therefore adjustment of HIV and AIDS therapeutic regimens becomes a rather complex problem.

Ethical Issues. Despite progress toward the provision of antiretroviral therapy, demand still outstrips availability, raising an ethical dilemma regarding for which populations the limited life-saving medications should be prioritized. A recent review of eligibility criteria used in Mexico, Senegal, Thailand, and Uganda¹⁵ outlines biomedical factors, adherence to treatment, prevention-driven factors, social and economic benefits, financial factors, and factors driven by ethical arguments as the criteria used. The review recommends that in order to ensure fair patient prioritization, widespread consultation with a variety of stakeholders, and not only policy-makers or physicians, is crucial.

In the case of clinical research studies that are conducted in resource-limited settings where antiretroviral therapy is not widely available, ethical issues may arise as to which patients to include in a study that may offer the only opportunity to access the life-saving therapy. This is in view of reported advantages of clinical trials in sub-Saharan African countries.¹⁶ At the same time, regulatory authorities may insist on guarantees for the availability of

therapy, hence the literature reports¹⁷ of creation of funds for postclinical trial access to antiretroviral drugs.

Lower Literacy Rates. An important social issue of concern for HIV pharmacotherapy delivery is the low rate of literacy in many sub-Saharan African countries. For example, Malawi has a literacy rate of only 59%, Zimbabwe 88%, and Botswana, Zambia, and Swaziland have rates of 76%, 77%, and 79%, respectively.¹⁸ Studies have shown a correlation between literacy rates and adherence to therapy in high-income countries. It is not clear whether these findings would hold true in resource-limited countries. A recent Canadian study evaluated estimates of antiretroviral therapy adherence in sub-Saharan Africa and North America.¹⁹ A meta-analysis of 31 studies from North America (28 full-text articles and 3 abstracts) and 27 studies from sub-Saharan Africa (9 full-text articles and 18 abstracts) was performed. The African studies represented 12 sub-Saharan African countries. The analysis found that favorable levels of adherence, much of which was assessed via patient self-report, could be achieved in sub-Saharan African settings and that adherence remains a concern in North America. Perhaps strong potential motivating factors such as the privilege of being offered life-saving medications improve adherence in these countries, regardless of low literacy rates.

Challenges to Resource Provision for Supporting HIV and AIDS Pharmacotherapy

Drug Financing

The Gross National Products (GNPs) per capita in most sub-Saharan African countries is low (see Table 2). Therefore, until recently, antiretroviral drugs have been beyond the economic reach of most.²⁰ Owing to economic hindrances, most of these countries have used a variety of strategies to address the issue of equitable access to antiretrovirals. Such strategies include adopting the World Trade Organization's Trade Related Intellectual Properties (WTO-TRIP) safeguards into national legislation, actively encouraging generic competition, seeking differential pricing of drugs from international suppliers, creating high volume and demand through regional procurement, and encouraging local production through licensing and technology transfer.²¹ These countries also addressed the issue of drug financing by seeking to balance the contributions from user fees, donors, and their own governments, as well as local health insurance agencies, bearing in mind that the HIV and AIDS epidemic is a public health problem.

At the international level the situation has shifted positively.²² In 2003 commitments were made to set up the Global Fund to fight AIDS, Tuberculosis, and Malaria. The President of the United States, as well as many philanthropists,

Table 2. Pharmacy Infrastructure in 5 African Countries in 1999

	Botswana	Malawi	Swaziland	Zambia	Zimbabwe
Total population (million)	1.5	11.0	0.9	10.2	12.4
GNP per capita (\$US)	6872	586	3987	756	2876
Number of pharmaceutical manufacturers/wholesalers	3	3	0	5	22
Number of registered drug products	340	1500	No DRA	1200	1700
Number of registered pharmacists	160	60	33	100	530
Number of registered pharmacy outlets	63	16	13	78	240

Adapted from World Health Organization study of drug regulatory authorities, 1999. GNP indicates gross national product; DRA, drug regulatory authority.

promised large sums of money to combat the spread of the epidemic. In December 2003 WHO/UNAIDS published a policy document outlining a plan to bring antiretroviral treatment to 3 million people in developing countries by the end of 2005. This document was termed the "3 by 5" initiative. It outlined how the WHO/UNAIDS intended to work with governments and groups to get treatment to where it is most urgently needed. Technical assistance to upgrade health care infrastructure and training and assistance to coordinate efforts to scale up treatment were provided under this initiative.

The "3 by 5" initiative brought about a marked increase in the accessibility of antiretroviral therapy to developing countries, particularly those in sub-Saharan Africa. According to the latest WHO/UNAIDS "3 by 5" data, by the end of 2006 more than 1.6 million people were on antiretroviral therapy, representing a 4-fold increase since December 2003. Overall, antiretroviral coverage in resource-limited countries increased from 7% in 2003 to 24% in June 2006.⁴

Drug Distribution Infrastructure

The HIV and AIDS epidemic has highlighted the weakness of health care systems in resource-limited sub-Saharan African countries in terms of referral systems, human resources, and laboratory capacity, as well as drug procurement and supply chains. Lack of capacity in the educational system has led to an overall shortage of qualified health personnel including pharmacists and pharmacy staff. In addition, loss of health professionals to the private sector, to metropolitan areas, to wealthier countries, and to the epidemic itself has starved the public sector in these countries of the people on whom delivery of antiretroviral therapy depends.

Most sub-Saharan African countries have a shortage of health care professionals, including pharmacy personnel. Table 2 summarizes data on pharmacy support infrastructure in the 5 heavily HIV-affected African countries of Botswana, Malawi, Swaziland, Zambia, and Zimbabwe. With the shortage

of fully qualified pharmacy personnel, drugs are primarily dispensed by untrained persons. Unregistered and unregulated drug stores or chemist shops are the major sources of prescription products being sold illegally in many of these countries. There is also a shortage of dispensary facilities that can coordinate pharmacotherapy management. Provision of antiretroviral drugs becomes particularly difficult under these circumstances because of the need for strict monitoring.

Innovative methods of delivering therapy that have been developed include utilizing specifically trained technicians, nurses, and lay community workers.²³ Furthermore, simplification of treatment regimens has allowed for a shift from a pharmacist-centered model to one that relies on team efforts that include nurses, medical assistants, and people living with HIV and AIDS who are employed and trained to perform community outreach and treatment support.

Government Commitment

The governments of sub-Saharan African countries initially struggled to accept the reality of the HIV and AIDS epidemic. South Africa ignored suggestions to adopt antiretroviral therapy as part of their national health policies, instead choosing to stir debate on whether HIV was the real cause of AIDS.²⁴ Recent reports suggest a significant shift toward accepting the reality of the need for antiretroviral therapy even though obstacles remain.²⁵

According to the recent WHO/UNAIDS report⁴ progress in expanding treatment and care provision in sub-Saharan Africa in the past year has been positive but uneven. At least one-third of the people in need of antiretroviral therapy are receiving it in such countries as Botswana and Uganda, while in Cameroon, Cote d'Ivoire, Kenya, Malawi, and Zambia between 10% and 20% of the people requiring antiretroviral drugs were receiving them in mid-2005. There is an extensive unmet need in most of the region. The WHO/UNAIDS reports that at least 85% (almost 900,000) of South Africans who needed antiretroviral drugs were not

yet receiving them in mid-2005. The same applied to 90% or more of those in need in countries such as Ethiopia, Ghana, Lesotho, Mozambique, Nigeria, Tanzania, and Zimbabwe.²⁶ Establishing an effective and efficient pharmacotherapy delivery system represents a great upcoming challenge for the governments of these countries.

Priorities in HIV and AIDS Pharmacotherapy

Emphasis on Prevention Versus Curative Therapy

As described above, approximately 90% of newly infected children in 2006 lived in sub-Saharan African countries, where the major route of infection is through mother-to-child transmission. As a result of the limited accessibility to antiretroviral therapy, the emphasis in sub-Saharan African countries is still largely on the prevention of HIV transmission. Therefore antiretroviral use is commonly found in prevention programs such as the prevention of mother-to-child transmission (PMTCT) and postexposure prophylaxis (PEP). Most sub-Saharan African countries have started integrating PMTCT in antenatal care services, although so far approximately only 1 in 4 pregnant HIV-infected women have access to those services.⁴

The long-term treatment regimens proven to work in wealthy countries are often not affordable in the sub-Saharan African countries. Therefore, shorter duration regimens are often implemented.^{8,9} For PMTCT, single-dose nevirapine given to the mother just before delivery is the most commonly used regimen.⁷ The WHO Technical Consultation has recently recommended regimens in the resource-limited world to include zidovudine alone, fixed-dose zidovudine/lamivudine, and nevirapine.

Management of Pediatric Versus Adult Population

The WHO/UNAIDS target of treating 3 million patients by the end of 2005 aimed to ensure that at least 10% to 15% of those patients would be infants

and children. One major obstacle that prevented the attainment of that target was that the medicines were not easily available in the appropriate formulations and at affordable prices. Lack of tools for forecasting requirements accurately made supply and procurement difficult, and pharmaceutical manufacturers seemed hesitant to invest in the development of pediatric formulations of antiretroviral products.

Challenges of treatment for HIV-infected children include the physiologic changes that occur during child growth that impact the pharmacokinetics of drugs. Palatability, chemical stability at various conditions found in resource-limited settings, and convenience of dispensing and dosing are also important considerations in pediatric pharmacotherapy, and are of particular importance in resource-poor settings where alternative options are few. Pediatric dosage regimens are usually based on either age or body surface area and can therefore be complicated. For example, zidovudine, nevirapine, and didanosine for infants each give dose requirements for body surface area. This is complicated in resource-poor settings where equipment, facilities, and trained staff are limited. A simplified weight-based method for pediatric drug dosing for zidovudine and didanosine in resource-limited settings has recently been published.²⁷

In the year 2000, one pharmaceutical company announced a 5-year program to provide nevirapine free of charge to resource-limited countries for the PMTCT of HIV. Since nevirapine was not used for this purpose in wealthier countries, the donated drug originally was provided without a suitable pediatrics package. Nevirapine suspension was only available in 240 mL containers even though only approximately 0.6 mL was needed for dosing for an infant. This posed difficulties in handling nevirapine for PMTCT programs, resulting in significant delays in the implementation of such programs that were meant to benefit from the donation program.²⁸

It should be noted that over the past few years along with the WHO/UN-

AIDS “3 by 5” initiative, significant efforts have been underway to address the above problem. The United States President’s Emergency Plan (PEPFAR), The Clinton Foundation, the Mother-to-Child Transmission (MTCT) Plus Initiative, The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), and other international non-governmental organizations (NGOs) have each developed specific programs to address the issue. In November 2004 the United Nations Children’s Fund (UNICEF) and WHO convened a meeting of technical experts to urgently identify ways and mechanisms to overcome key obstacles to access of appropriate, acceptable, and affordable antiretroviral formulations for children.²⁹

Médecins Sans Frontières addressed this issue in its campaign for access to essential medicines.³⁰ In its pricing guide for antiretroviral drugs for resource-limited countries it is recognized that certain pediatric solutions such as syrups are not always the most appropriate in resource-limited settings. Alternative options, including low-dosage capsules that can be opened and mixed with food and dosage-dispersible tablets should be considered for sub-Saharan African countries.

Emphasis on Affordable Versus the Most Effective Available Regimens

When antiretroviral medications become widely available in the sub-Saharan African countries the use of affordable drugs should be of high priority.³⁰ As discussed earlier, there is a great emphasis on exploring strategies to enable equitable access to drugs. This includes encouraging generic competition, adopting WTO-TRIP safeguards into national legislation, bulk regional procurement, and encouraging local production through licensing and technology transfer. The use of formularies or essential drug lists (EDLs) also promotes availability of the drugs. However, cost is a major criterion for a drug product to be listed in EDLs in sub-Saharan African countries. Therefore, antiretrovirals are easily omitted from these EDLs and are not included as part of their health policies.

Focusing on essential generic medicines in sub-Saharan African countries is in sharp contrast with the situation found in wealthy countries such as the United States, where the most effective regimens available on the market are sought in spite of their high cost. Antiretroviral therapy is often individualized for the specific needs of the patient in the United States and in most European countries because most drugs available on the market are accessible. Patients with HIV infection are prescribed the newest antiretrovirals available, not always due to necessity, but as a result of treatment individualization or even pharmaceutical marketing.

Concerns with Counterfeit and Substandard Products

The shortage of essential drugs in combination with high prices raises concerns regarding counterfeit drugs. Many resource-limited sub-Saharan African countries have underdeveloped drug regulatory systems that are vulnerable to counterfeiting of drug products.³¹ Although this problem can affect developed countries as well, they often have the means to deal with it promptly. The challenge remains for sub-Saharan African countries to ensure that genuine products are distributed on their markets.

With the use of generic antiretroviral products also comes the concern of quality. Patent laws are often overridden well before the normally stipulated 20 years to allow for distribution of generic antiretrovirals due to the HIV and AIDS public health emergency. Information on the pharmacologic properties of the innovator (branded) drugs is therefore often not widely available by the time the generic forms of antiretrovirals enter the market. In addition, generic drugs may be produced using methods that differ from those of the innovator brands, leading to the potential for impurities and instabilities. There is a need to ensure that generic products are bio-equivalent to the innovator products.³² Prequalification of generic manufacturers and postmarketing quality and bio-equivalence surveillance systems in sub-Saharan African countries have been recommended.

Prospects and Opportunities for International Collaboration

Reports have appeared on ways of fostering international collaboration for the transfer of technical and logistic support in various health-science related areas including an oral health research collaboration in Guatemala,³³ a collaborative biomedical research network in Brazil,³⁴ global collaboration in epidemiology,³⁵ and a pilot telemedicine project in Western Africa.³⁶ Training of local personnel for sub-Saharan African countries is also being advocated as a way to ensure sustainable scaling up of the response to HIV and AIDS.¹⁶

In the areas of HIV pharmacotherapy, a growing number of international organizations are being developed to assist in sub-Saharan African countries. Generally, these groups focus on strengthening human resource capacity, developing common education strategies for prevention of HIV transmission, treating and preventing opportunistic infections, and recently, providing antiretroviral therapy.³⁷

The National Institute for Allergy and Infectious Diseases (NIAID) and other international advisory groups such as UNAIDS have identified the need to increase the capacity of resource-limited countries to undertake HIV and AIDS research.^{12,38} This has resulted in such initiatives as the Comprehensive International Program of Research on AIDS (CIPRA)⁵ and the AIDS International Training and Research Program (AITRP).³⁹ These initiatives are aimed at supporting fundamental research on interventions relevant to resource-limited countries, enabling them to enhance their research capabilities. The same initiatives also generate knowledge and resource bases that benefit all nations.

The International Center for HIV/AIDS Pharmacotherapy Research and Training (ICHAPRT) is an initiative from the School of Pharmacy and Pharmaceutical Sciences at the University at Buffalo in collaboration with the School of Pharmacy at the University of Zimbabwe. The HIV ePharmacotherapy Network (www.hiv.buffalo.edu) at the University at Buffalo en-

hances expertise among caregivers, educators, and researchers in HIV and AIDS and establishes an interactive forum for knowledge advancement and patient care.

ICHAPRT identifies methods that have been successful in developed countries and, through formalized training and educational initiatives, seeks to transfer these approaches to Zimbabwe. Examples of such areas include the promotion of sustainable access to essential drugs (antiretrovirals and medications for opportunistic infections) as well as pharmacotherapy research topics such as adherence to therapy, clinical pharmacokinetics, adverse drug reactions, drug interactions, pharmacogenomics, and therapeutic drug monitoring. Several joint research and clinical service programs have been implemented with the involvement of visiting scholars. Notable achievements so far include the implementation of a community-based adherence support program,^{40,41} capacity building for quality and bioequivalence surveillance of generic antiretrovirals, and the development of a Website covering international perspectives. These endeavors have laid the groundwork for further international collaborations.

Summary

In the area of HIV pharmacotherapy in resource-limited settings, particularly in sub-Saharan Africa, countries possess specific issues and challenges that need to be well understood and taken into consideration when setting priorities for collaborative efforts. Many resource-limited countries are too preoccupied with other issues to address the accessibility of good quality products that are appropriate for their specific patient populations. Understanding these disparities could lead to more effective collaboration linkages. Academic institutions are best placed to lead in the development of such partnerships since they seek the same goals of information generation and dissemination.

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