The growing challenge of HIV/AIDS in developing countries

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The burden of HIV infection and disease continues to increase in many developing countries. An emerging theme is of an HIV pandemic composed of mini-epidemics, each with its own characteristics in terms of the trends in HIV prevalence, those affected, and the HIV-related opportunistic diseases observed. A number of explanations for the observed differences in the spread of HIV infection have been proposed but since the factors concerned, such as sexual behaviour and the prevalence of other sexually transmitted diseases, are closely interrelated, it is difficult to tease out which are the most important. Among HIV-related opportunistic diseases, tuberculosis stands out as the most important cause of morbidity and mortality in most developing countries, but the relative prevalence of other diseases shows considerable regional variation. Thus, there is a need for local approaches to the global problem of managing HIV disease. The most pressing public health challenges are to use existing knowledge of strategies to reduce HIV transmission, and to apply them in ways appropriate to the local situation, and to develop, evaluate and implement interventions to prolong healthy life in those already infected.

The human immunodeficiency virus (HIV) pandemic has emerged, over the 16 years since the first description of a cluster of cases of Pneumocystis carinii pneumonia (PCP) among homosexual men in Los Angeles¹, to become one of the most important global public health challenges of recent times. Since the start of the epidemic, issues around HIV and the acquired immunodeficiency syndrome (AIDS) have had a high profile in industrialised countries. However, the burden of disease continues to fall most heavily, and often less visibly, in developing countries, particularly in Africa. In industrialised countries, the recent introduction of highly active antiretroviral therapy has raised hopes of substantially improved prognosis for HIV-infected individuals. By contrast, in developing countries, very little has happened to improve the gloomy outlook, particularly for those with symptomatic disease who have reached the stage of severe immunosuppression.
In this article, we review the current global situation of the HIV/AIDS pandemic, highlighting the regional differences in epidemiology that are becoming apparent, exploring possible reasons for this heterogeneity and outlining the challenges that HIV/AIDS presents to public health in the developing world.

### The current situation

#### Burden of HIV infection

The World Health Organization (WHO) estimated that, at the end of 1997, 30.6 million people worldwide were living with HIV/AIDS, of whom over 90% were in developing countries, two-thirds in sub-Saharan Africa. An emerging theme in the global epidemiology of HIV is of regional variation; thus the global pandemic is composed of different regional or local epidemics, each with its own characteristics. For example, within the countries of sub-Saharan Africa, there are substantial differences in the observed trends in HIV prevalence. These are most often compared using data from pregnant women, despite potential difficulties in assuming that HIV prevalence in pregnant women is representative of that in the general population.

Trends in HIV prevalence in selected countries in sub-Saharan Africa are illustrated in Figure 1. In some central and west African cities, such as Kinshasa and Yaoundé, HIV prevalence seems to have remained stable at relatively low levels. By contrast, in other countries, particularly in eastern and southern Africa, there has been an explosive rise in prevalence to much higher levels. These differences cannot be

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**Fig. 1** Trends in HIV prevalence among pregnant women in selected cities in sub-Saharan Africa. Adapted from Buvé et al. with additional data from the US Bureau of the Census.
accounted for simply by differences in the duration of the epidemic. For example, the first AIDS cases in Kinshasa, Lusaka and Kampala were all observed in 1983; HIV prevalence has increased dramatically in Lusaka and Kampala, but not in Kinshasa.6

There are some encouraging data which suggest that the situation may be improving in some countries. Declining HIV prevalence has been reported in a rural population cohort in Uganda7, and among military recruits in Thailand8, both of which have been attributed to changes in sexual behaviour. However, an alternative explanation for the falling prevalence in Uganda is maturing of the epidemic, with falling prevalence accounted for by high mortality in the presence of stable and high incidence9. Stabilisation or decrease in HIV prevalence is far from universal. Over the same time period, rapid increases in HIV prevalence have been observed in India, Vietnam, Myanmar (Burma) and South Africa2-10, and it is predicted that South Africa will experience one of the worst HIV epidemics in Africa11.

**Burden of HIV-related disease**

Estimates of the cumulative numbers of AIDS cases point to the burden of disease falling most heavily in developing countries, particularly sub-Saharan Africa, which is thought to have accounted for 5 million of the cumulative total of 6.7 million AIDS cases from the late 1970s to the end of 199612. In other developing countries, particularly those in Asia, the epidemic started later and so the burden of AIDS cases may be expected to increase sharply over the next few years. In some countries where the epidemic is well established, HTV infection is the leading cause of death among adults13,14.

**Spectrum of disease: causes of morbidity and mortality**

In industrialised countries, the spectrum of HIV-related disease is well described: in the US and Europe, the most frequent AIDS-defining disorders are PCP, Kaposi's sarcoma and oesophageal candidiasis15,16. There are far fewer data from developing countries, largely because of lack of access to the necessary diagnostic facilities.

In Table 1, the relative frequencies of HIV-related opportunistic infections among hospitalised patients in Africa, South America and Asia are compared. It is difficult to make direct comparison between these studies because of differences in methodology. In the two studies from Africa, patients admitted to hospital were recruited systematically, regardless of HIV status or clinical presentation. In the other studies,
only patients classified as having AIDS were included and, hence, severe illness in HIV-infected patients who did not fulfil the AIDS case definition would have been underestimated. In some studies, only diseases classified as HIV-related were enumerated: in particular, blood cultures were performed systematically in both African studies, and in most patients in the Thai study, but not in the others. This is the most likely explanation for the high prevalence of bacteraemia in the African and Thai studies and its absence in the others. In Table 2, data from three autopsy studies from Côte d’Ivoire, Zaire and Mexico are compared. Again, caveats are necessary when making comparisons: the study from Côte d’Ivoire includes all HIV-infected patients regardless of their clinical presentations, whereas the other two include only patients with a clinical diagnosis of AIDS. In addition, there may be differences
Table 2  Prevalence of opportunistic diseases identified at autopsy of HIV-infected adults in different developing countries

<table>
<thead>
<tr>
<th>Region</th>
<th>Sub-Saharan Africa</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Côte d'Ivoire</td>
<td>Zaire</td>
</tr>
<tr>
<td>Reference No.</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Population</td>
<td>HIV+ patients dying in hospital</td>
<td>Patients with AIDS dying in hospital</td>
</tr>
<tr>
<td></td>
<td>247</td>
<td>63</td>
</tr>
</tbody>
</table>

No. HIV+ patients

- Tuberculosis (%): 38, 41*, 25*b
- Bacterial pneumonia (%): 30, 34, 11
- Cytomegalovirus (%): 18, 13, 69*c
- Bacteraemia (%): 16, –, –
- Cerebral toxoplasmosis (%): 15, 11*d, –
- Non-specific enteritis (%): 10, –, –
- Kaposi's sarcoma (%): 9, 16, 30
- Nocardiosis (%): 4, –, 1
- Cryptococcosis (%): 3, 19*, 11
- Atypical mycobacteriosis (%): 3, –, 6
- PCP (%): 3, <2, 24
- Cryptosporidiosis (%): 3, <2, 7
- Non-Hodgkin's lymphoma (%): 3, –, 5
- Histoplasmosis (%): 2, <2, 10
- Candidiasis (%): –, 31f, 5g

* Mycobacterial disease, extrapulmonary, probably Mycobacterium tuberculosis; b disseminated tuberculosis; c cytomegalovirus infection, disease not specified; d brain only available in one case – 10% disseminated toxoplasmosis, 1% cerebral; e cryptococcoses, extrapulmonary; f candidiasis, esophagus or trachea; g oral and oesophageal candidiasis, and fungal pneumonia.

in the definition of specific diseases, particularly with respect to cytomegalovirus and candidiasis.

Despite the difficulties in making comparisons, it is striking that in almost every study from developing regions, tuberculosis is the most frequently identified opportunistic disease. There are marked variations in the prevalence of other diseases usually regarded as HIV-associated. This may be due partly to differences in ascertainment, but data from other studies support the idea that there are important regional variations in HIV-related diseases; for example PCP, which is relatively common in Central and South America20,21,26 and in Thailand23, but rare in most African countries27. The implications are that tuberculosis control is a major priority in limiting the effects of HIV on public health in developing countries in all regions, but that differences in the relative prevalences of other opportunistic diseases mean that guidelines for appropriate presumptive treatment and prophylaxis for HIV-infected individuals should be region-specific28.
Reasons for heterogeneity of the epidemic

Proposed explanations for regional variations in the HIV epidemic may be divided into factors which may influence HIV prevalence and those which may influence the clinical manifestations of HIV disease.

Heterogeneity in HIV prevalence

**Virus factors** There are striking differences in the epidemiology of the two types of human immunodeficiency virus: HIV-1 has caused a global epidemic, whereas HIV-2 has remained largely confined to west Africa, where its prevalence is stable or declining. It is therefore plausible that differences between the subtypes of HIV-1 may contribute to regional differences in epidemiology. In Thailand, a case-control study suggested that there might be increased heterosexual transmission of subtype E compared with subtype B, although it was not possible to control for the effect of the mode of HIV acquisition (sexual or intravenous drug use). Subtype A is predominant in all parts of sub-Saharan Africa except for South Africa and Malawi, and so differences in subtype alone cannot account for the marked differences in HIV prevalence observed in African countries.

**Host factors** Host factors are generally thought to be the most important determinants of global differences in the epidemiology of HIV infection. These can be divided into, first, factors that influence the risk of exposure to HIV, such as patterns of sexual mixing, the extent of concurrent sexual partnerships and rate of partner change; and second, factors which influence the risk of transmission of HIV during contact with an infected individual, including sexual practices, the prevalence of other sexually transmitted diseases, circumcision, condom use, and the stage of HIV disease of the infected individual.

Existing data demonstrate regional differences in some of these factors, but their relative importance is difficult to determine, not least because many of them are interrelated, such as sexual behaviour and the prevalence of sexually transmitted diseases. A multicentre study to explore the role of differences in sexual behaviour, the prevalence of sexually transmitted diseases and circumcision in determining differential spread of HIV infection in Africa is currently in progress: this is a collaborative project between the Institute of Tropical Medicine in Antwerp, the London School of Hygiene and Tropical Medicine (LSHTM), INSERM and UNAIDS.

In addition, studies of individuals who remain seronegative despite being highly exposed to HIV suggest that there may be biological factors...
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which confer protection against infection (‘natural immunity’) although the mechanism for this phenomenon is unclear.

Environmental factors Environmental factors which may influence the spread of HIV infection include societal factors such as socio-economic status, urbanisation and migration, the stage of the HIV epidemic in the population (since this may affect infectiousness), differences in duration of survival with HIV infection (since the prevalence of a disease is related to its duration) and societal responses to the epidemic.

Migrant populations are particularly vulnerable to HIV infection. In West Africa, the migration of agricultural workers to all-male camps, where many men share the services of a small number of female prostitutes, results in a pattern of sexual mixing which promotes the spread of HIV infection. Women also migrate in search of employment, for example Ghanaian women to neighbouring Côte d’Ivoire, where many work as prostitutes. Côte d’Ivoire is the major destination for migrant workers in West Africa, and this may be one of the reasons why it has the highest HIV prevalence in the region. The observed trends in HIV prevalence in Abidjan are consistent with migration being an important contributor to the epidemic: the male:female ratio of AIDS cases was 4.8:1 in 1988, but had fallen to 1.9:1 by 1993, consistent with the early epidemic being concentrated among a core group of female sex workers and their male clients.

HIV and developmental issues are also closely linked. The highest HIV prevalences are seen among those who are poor, marginalised or displaced, and the most likely consequence of the HIV epidemic in developing countries is to increase the gap between rich and poor.

Heterogeneity in spectrum of disease

Environmental factors Environmental factors are likely to be the most important determinants of regional differences in the prevalence of HIV-related diseases. The majority of adults in developing countries are infected with tuberculosis, and the development of HIV infection provides the strongest known risk factor for the development of tuberculosis disease. It is, therefore, not surprising that tuberculosis is the most common HIV-related disease in most developing countries, but is less prevalent in industrialised countries where infection with tuberculosis is less widespread.

In African countries, bacterial infections are the second major cause of HIV-related disease. The high prevalence of disease due to enteric pathogens such as non-typhoid salmonellosis is probably attributable to the overcrowded, insanitary living conditions associated with poverty in
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many developing countries. HIV-related diseases caused by pathogens which have a restricted global distribution, such as *Penicillium marneffei* in southeast Asia, are confined to HIV-infected individuals in those regions.

The regional differences in the prevalence of PCP are harder to understand. As shown in Tables 1 and 2, PCP is a common HIV-related illness in those countries in Latin America, India and southeast Asia where appropriate studies have been carried out. In Africa, PCP has been identified in HIV-infected adults and children in autopsy studies and in adults with respiratory disease. However, it is less important as a respiratory pathogen than tuberculosis and bacterial infections.

In a study from Abidjan, Côte d'Ivoire, most HIV-infected adults hospitalised with respiratory disease had CD4 counts below 200 x 10^6/l. It is, therefore, unlikely that the reason for the lack of PCP in African populations is because patients die of other diseases before they reach the level of advanced immunosuppression at which PCP occurs.

Host factors Host factors may influence the expression of some HIV-related diseases. For example, Kaposi's sarcoma-associated herpes virus (HHV-8) has been identified from a high proportion of Kaposi's sarcoma lesions in a number of populations. The seroprevalence of HHV-8 among HIV-negative persons who do not have Kaposi's sarcoma is much higher in Uganda than in North America. It remains to be determined whether the association between HHV-8 and Kaposi's sarcoma is causal, and if so what factors determine whether Kaposi's sarcoma develops in HHV-8-infected individuals. Among heterosexual populations, the higher prevalence of Kaposi's sarcoma in men than women suggests a hormonal influence on susceptibility to tumour development.

An individual's HIV transmission category may also influence susceptibility to opportunistic disease. Among HIV-infected individuals in Thailand, intravenous drug users were more likely to have tuberculosis and bacterial infections, and less likely to have cryptococcal meningitis and PCP compared with those who were infected by sexual transmission.

Public health challenges

Prevention of HIV infection

The great majority of HIV infections worldwide are heterosexually transmitted, and a number of strategies have already been shown to be effective in reducing sexual transmission. For example, at the individual
level, consistent condom use reduced transmission between HIV-discordant couples; at the community level, improved management of sexually transmitted diseases reduced HIV incidence; and at the national level, campaigns in Thailand promoting condom use seem to have been effective in changing sexual behaviour and reducing HIV incidence. Successful programmes to prevent sexual transmission need to integrate condom promotion, behaviour change and control of sexually transmitted diseases: other important strategies include the provision of voluntary counselling and testing services, youth interventions and education for girls. The main priority in reducing the sexual transmission of HIV is to ensure that strategies of proven effectiveness are applied in a way appropriate to the local situation.

As more women become infected with HIV, mother-to-child transmission becomes an increasingly important problem. The ACTG076 trial showed that mother-to-child transmission can be reduced using a complex regime of zidovudine. The zidovudine regime as used in this trial is neither feasible nor affordable for most women in developing countries, and trials are underway to evaluate the efficacy of more practical regimes. Breast feeding has been shown to confer an additional risk of HIV transmission to children who are uninfected at birth but, in populations that have difficulty in preparing formula feed safely, the relative risks and benefits of early weaning need to be investigated.

In industrialised countries, strategies to reduce HIV transmission by blood transfusion have been highly effective, and less than 0.1% of infections are transmitted by this route. However, the same success has not been achieved in all regions: in many African countries, about 10% of new HIV infections are attributable to blood transfusion. Reduction of HIV transmission by this route requires that blood is transfused only when it is essential to save life; that blood is donated by unpaid, altruistic volunteers, with exclusion of potential donors at high risk of recent HIV infection; and that donated blood is screened for HIV antibodies using a test with high sensitivity.

Mitigation of HIV disease

Most public health strategies in developing countries to date have justifiably focussed on prevention of HIV transmission. However, the increasing burden of HIV disease in many countries cannot be ignored. There is a continuing lack of basic epidemiological data concerning the relative prevalences of opportunistic infections in many regions, for example southern Africa, and without such data it is difficult to develop appropriate strategies for the management and prevention of HIV-related
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disease. It is clear, however, that tuberculosis is the major cause of HIV-related disease in the majority of developing countries, and improving the control of tuberculosis is vital to protect the health of both HIV-infected and uninfected individuals.

Management of other HIV-related diseases in resource-poor settings is made difficult by the lack of laboratory facilities, without which precise diagnosis is often impossible, and the prohibitive cost of treatment of many opportunistic infections. Clinical algorithms for diagnosis and management of the opportunistic diseases most prevalent in a particular region need to be developed and tested, and essential drugs lists implemented. Prophylactic regimes aimed at preventing the most common opportunistic infections in a particular region need to be evaluated.

The use of antiretroviral treatments in developing countries is an issue which is increasingly pressing. The dramatic short-term benefits of highly active antiretroviral therapy seen in industrialised countries draw attention to their unavailability to the majority of people in countries where the burden of HIV disease is heaviest. In reality, the newer antiretrovirals are already available to a privileged minority in many resource-poor countries, and there is concern that incorrect use of these treatments could lead to the development of resistance, rendering the drugs useless. Discussion of these difficult issues needs to continue with the aim of reversing the trend of increasing inequality between rich and poor countries in access to effective treatment.

Research priorities

Priorities for research on HIV prevention in developing countries include evaluation of female-controlled methods to prevent sexual transmission of HIV, such as vaginal microbicides, developing practical strategies to improve the control of sexually transmitted diseases, and developing and evaluating programmes to promote sexual health among adolescents; evaluation of feasible antiretroviral regimes to reduce mother-to-child transmission in developing countries; and examining the relative risks and benefits of breast feeding in different situations.

Priorities for the mitigation of HIV disease include defining the spectrum of HIV-related disease in different regions; developing and evaluating clinical algorithms for diagnosis and management of common HIV-related conditions, and primary prophylactic regimes directed against the most prevalent opportunistic infections in specific regions; and working towards effective and sustainable use of antiretroviral therapy in resource-poor countries.

Perhaps the greatest challenge is to avoid becoming discouraged in the face of a problem which may seem overwhelming. To quote someone...
living with HIV/AIDS, on the subject of access to antiretroviral treatments: *This is not an overnight process. Let us build slowly. Each day and each month, more people will have access to antiretrovirals. Let us take it a step at a time, a day at a time – the way I live my life*.61

**Acknowledgments**

ADG was an MRC Training Fellow. Additional funding for work in Abidjan was received from the Roche African Research Foundation and the Rockefeller Foundation.

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