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FURTHER EDUCATION SERIES—HIV

Management of HIV in resource-poor countries, with a focus on sub-Saharan Africa

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Summary HIV/AIDS is the modern world's greatest pandemic, the brunt of which falls on sub-Saharan Africa. HIV/AIDS control efforts have up till now focused mainly on prevention, with little attention paid to care. This approach must change, and prevention has to be linked with an essential package of care if there is to be any hope of reducing HIV incidence rates or curbing the morbidity and mortality associated with AIDS. The package of care includes psycho-social support, screening for sexually transmitted infections and tuberculosis, clinical care for opportunistic infections, palliative care for terminal illness, home based care, care and support for orphans, prevention of mother to child transmission of HIV, preventive therapy and the possibility of antiretroviral (ARV) drugs. Many countries in sub-Saharan Africa are developing plans to scale-up treatment and prevention programmes, including the use of ARV drugs. However, any meaningful challenge to the AIDS epidemic requires a huge scale-up of support from the international community, both for ARV drugs and for basic prevention and care packages.

Introduction

HIV/AIDS has become the modern world's greatest pandemic. Twenty years after first being recognized, it has claimed 22 million lives and created 13 million orphans.[1] Sub-Saharan Africa bears the brunt of this global catastrophe. With less than 10% of the world's population, the region is home to 70% of people living with HIV/AIDS (25·3 million). In sub-Saharan Africa in the year 2000, there were 3·8 million new HIV infections and 2·4 million people with HIV/AIDS died, representing 80% of global AIDS deaths for that year. This review will focus on the current management of HIV in resource-poor countries of sub-Saharan Africa, and discuss the shortfalls and the ways forward.

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Table 1. HIV/AIDS prevention activities

Preventing sexual transmission of HIV
Mass media campaigns
Education of youth and school children
Condoms, condom promotion, condom social marketing
Treatment of sexually transmitted infections
Preventing mother-to-child transmission of HIV
Antiretroviral therapy
Non-antiretroviral interventions
Elective Caesarean sections (dubious role in Africa)
Safe alternatives to breast feeding (hard to find)
Screening of blood for transfusion
HIV voluntary counselling and testing (VCT) services
Rapid whole blood testing
Good quality pre-test and post-test counselling

Preventing HIV

The main efforts of National AIDS Control Programmes in sub-Saharan Africa have centred around prevention of HIV (Table 1). The strategies for preventing sexual transmission of HIV have concentrated on use of condoms, treating sexually transmitted infections (STI) and reducing unsafe sexual behaviour. These strategies have had some success in reducing the growth of the epidemic in selected populations,[2–4] but on a wider scale the impact is less convincing. STI service provision remains a neglected health issue, consistent condom use is rare and sexual vulnerability of women is still high.

Rates of mother to child transmission of HIV, without any intervention, are estimated to be 20–40% in sub-Saharan Africa.[5] Nevirapine, a non-nucleoside reverse transcriptase inhibitor, given as a single 200 mg dose to an HIV-infected mother at onset of labour, followed by 2 mg/kg to babies within 72 h of birth reduces HIV transmission to about 8% at birth.[6] This regimen offers the least expensive and simplest antiretroviral (ARV) intervention for resource-poor countries, with significant efficacy maintained in breast-feeding infants up to 4 months of age. However, few countries have begun to adopt this as a routine intervention, despite nevirapine being offered as a donation from the pharmaceutical company. The offer of donated nevirapine is conditional upon the provision of good antenatal care and HIV voluntary counselling and testing (VCT), both of which may be barriers to widespread implementation. Breast-feeding itself facilitates HIV-transmission, the risk after 4 months of age being estimated at approximately 3% per year.[7] However, for the foreseeable future, breastfeeding is likely to remain the norm because safer alternatives are hard to find.

Despite an almost universal policy in the region to screen donated blood for HIV, the risk of HIV transmission by blood transfusion may still be substantial[8]. Some of the reasons include the window period of infection, laboratory errors, HIV-1 group O isolates and interrupted supplies of HIV test kits.

A key factor underpinning any HIV prevention strategy is accessibility to voluntary counselling and testing (VCT) services. VCT has been shown to be cost-effective in promoting behaviour change and reducing sexual transmission of HIV.[9,10] Uganda is one of the few African countries which has provided low-cost, high quality and wide-scale VCT services, and this is believed to be one of the important factors in the country's success in

HIV prevention. Unfortunately, in most of sub-Saharan Africa few people have access to good quality VCT services, and it has been estimated that nearly 90% of infected people do not know their HIV status.[11] Same-day HIV testing strategies, using rapid whole blood tests, provide a simple, though costly, intervention which may make VCT more client-friendly than before, and facilitate a better uptake of the service.

Management and care of HIV-related disease: current status

In industrialized countries, the diagnosis of HIV is based on informed consent, pre-test counselling, ELISA screening and confirmatory tests, and post-test counselling. A CD4-T-lymphocyte count is a pivotal test for evaluation of any patient with HIV infection, and quantitative plasma HIV RNA is used for staging and monitoring response to ARV therapy. The standard of care is highly active antiretroviral therapy (HAART), using a combination of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. These are administered on an individual patient basis with regular monitoring for viral drug resistance. HAART has transformed AIDS from a fatal disease with a short time course into a treatable and chronic condition.[12] HAART is supplemented by chemoprophylaxis for opportunistic infections, the current best treatment for opportunistic infections and HIV-related tumours when they arise, and care by a physician with HIV-disease experience.

The contrast in most countries in sub-Saharan Africa could not be more striking. Many patients are diagnosed with AIDS on clinical grounds, and HIV serological testing is often not carried out. Where HIV testing is performed, it is often an ELISA and only one test is carried out. There are no routine measurements of CD4 cell counts or HIV RNA. It is estimated that only 25,000 (0·1%) of Africa's 25 million HIV-positive individuals receive any ARV therapy whatsoever, and many of these receive drugs in a chaotic and unregulated manner within the private sector with grave consequences for the development of drug resistance.[13] There is minimal use of chemoprophylaxis against opportunistic infections, there are few facilities to diagnose conditions such as *Pneumocystis carinii* pneumonia or cerebral toxoplasmosis and no specific drugs in the routine health service to treat serious conditions such as cryptococcal meningitis or Kaposi's sarcoma.

Research studies in sub-Saharan Africa have shown that the spectrum of disease differs from that seen in industrialized countries with tuberculosis (TB), pneumococcal disease, chronic diarrhoea, deep-seated pyogenic infections and bacteraemia being responsible for much morbidity and mortality.[14,15] Late stage diseases such as *Mycobacterium avium* complex or cytomegalovirus are rare, possibly because patients die earlier on from other more aggressive infections. Despite these potentially treatable infections, studies in central and east Africa have shown considerable HIV-related adult mortality and substantial reduction in life expectancy in urban and rural settings.[1,11] In rural Uganda, median survival from time of diagnosis of HIV was 4–5 years and median survival after the onset of AIDS was 9 months.[16]

Management and care of HIV-related disease: ways forward

Prevention efforts have not been successful in high HIV-epidemic countries because of a lack of understanding that prevention needs to be linked with care, and the dogmatic unwillingness

Table 2. An essential package of care for HIV/AIDS patients'

Diagnostic HIV testing with pre- and post-test counselling
Psycho-social support/home base-care/palliative care
Screening for sexually transmitted infections and TB
Treatment for opportunistic infections
Care and support for orphans
Orphanage care
Orphan living assistance
Orphan's school fee assistance
Prevention of opportunistic infections
Cotrimoxazole preventive therapy
Isoniazid preventive therapy
Highly active antiretroviral therapy (HAART)

to commit resources for treatment. Health sectors need to develop and implement a comprehensive package of care for patients with HIV-related disease (Table 2), and this should compliment prevention efforts. The package needs to be centred around good quality VCT, which should act as the pivot for easy and rapid referral to the other support services offered in the 'essential care package'. Provision of a continuum of care is essential, with a two-way referral system between health facilities and the community. Three aspects of the essential care package need further discussion: treatment of opportunistic infections and HIV-related tumours, prevention of opportunistic infections and ARV therapy.

Treatment of opportunistic infections and HIV-related tumours

Most countries will have developed their own guidelines for the clinical management of HIV-related disease, based on generic guidelines produced some years ago by the World Health Organization (WHO).[17] These guidelines often use clinical algorithms, based on the acknowledgement that diagnostic facilities are poor and the drug armamentarium is limited. For example, chronic diarrhoea caused by *Cryptosporidium, Isospora belli, Microsporidia* or other pathogens would be treated sequentially with cotrimoxazole, metronidazole and albendazole, depending on the response. Tuberculosis is one of the commonest HIV-related opportunistic infections in Africa, and in general is well managed through the WHO Directly Observed Treatment, Short Course (DOTS) Strategy. About 60% of TB cases in Africa are treated under a DOTS programme, and 63% of such cases successfully complete treatment.[18] Cryptococcal meningitis affects around one in 10 patients with AIDS. Without treatment (and this is the norm), life expectancy is less than 1 month[19]. Fluconazole is the key drug in this situation, and Pfizer have announced that it will make donations to sub-Saharan Africa to increase its accesssibility for patients.

The commonest HIV-related tumour is Kaposi's sarcoma. There are a number of treatment options ranging from radiotherapy, cytotoxic agents (for example, vincristine) and alpha-interferon, but most of these are too expensive for the majority of patients with the disease.

Prevention of opportunistic infections

COTRIMOXAZOLE PROPHYLAXIS

Preventive therapy for HIV-related opportunistic infections is currently based on the use of cotrimoxazole, although the efficacy of other antibiotics (such as ciprofloxacin) and multivitamins/micronutrients are being assessed in controlled trials. In Cote d'Ivoire, cotrimoxazole significantly reduced the case fatality rate in HIV-positive TB patients[20] and reduced morbidity in HIV-infected patients without TB.[21] As a result of these studies, UNAIDS made provisional recommendations that co-trimoxazole should be given to all patients in Africa living with AIDS.[22] However, it would be prudent to gather more evidence about the efficacy of this intervention in other parts of Africa because of different pathogens and drug resistance profiles. Even if co-trimoxazole is effective, its widespread use by AIDS patients may have adverse consequences for the treatment of acute respiratory infections in children (co-trimoxazole is first line therapy) and for the treatment of malaria in countries which use sulphadoxine-pyrimethamine as their first-line treatment.[23] Thus, it might be wise to confine cotrimoxazole prophylaxis to those who will benefit most from it. A study in South Africa showed that cotrimoxazole conferred a survival advantage to those who had significant immunosuppression (WHO stages 3 and 4), but there was no significant effect in those with WHO stage 2 disease.[24]

ISONIAZID PREVENTIVE THERAPY

TB is one of the major opportunistic infections in HIV-positive individuals. Isoniazid, given as primary preventive treatment to reduce the incidence of TB in HIV-positive persons, has been shown to be efficacious at least in the short to medium term in well-conducted studies.[25] Secondary isoniazid preventive therapy after HIV-positive patients have completed a course of anti-TB treatment also significantly reduces the risk of recurrent TB.[26] There are currently doubts about how feasible and effective isoniazid preventive therapy will be as a TB control strategy. Nevertheless, it should be part of the essential package of care offered to individuals who wish to know their HIV status.

Antiretroviral (ARV) therapy

The one therapy likely to have a major impact on morbidity and mortality associated with HIV/AIDS is HAART. There is also evidence that lowering the viral load with HAART may reduce the likelihood of transmitting HIV infection to others.[27] The main reasons given to date for the lack of availability of HAART in Africa have been the high cost of the drugs and the perceived inability of the health infrastructure to manage the complexities of treatment.

This state of affairs might change. Pharmaceutical companies have significantly reduced the cost of ARV drugs, and drug companies in India, Brazil and Thailand are producing cheap generic versions.[28] These are welcome initiatives, but for very poor countries which spend less than US$5 per capita per year on health, ARV drugs are still too expensive unless there is additional assistance from the international community.

ARV drugs must not only be accessible, but they must be provided within a structured framework. It has been argued that the structure used to deliver and monitor anti-tuberculosis treatment to TB patients throughout the developing world could be a model for delivering

Table 3. Antiretroviral policy package

Sustained government and political commitment:
Nationwide coverage
Central-regional-district units
Full integration into the health system at all levels
Antiretroviral drugs as part of an essential package of care for HIV/AIDS patients
Case detection through passive case finding by ensuring access to quality-assured VCT:
Focus on HIV-positive patients with symptoms who have undergone VCT (e.g. those fulfilling WHO case definition for AIDS in Africa)
Administration of standardized antiretroviral regimens under proper case management conditions including direct observation of treatment:
Choice depends on simplicity, efficacy, cost, safety
Once a day administration preferable
Protease inhibitors best avoided because of interactions with rifampicin
Need first and second line regimens in case of adverse effects and development of drug resistance
Establishment of a regular supply of quality assured drugs:
Need reliable drug procurement, distribution and security systems
Recording and reporting system:
Monitor progress of individual patients as well as programme performance

ARV therapy.[29] The strategy would be to use standardized, combination ARV therapy for HIV-positive patients with symptoms. The targets for ARV therapy would be lifelong treatment once the patient has started HAART and drug adherence rates of 90% or greater to minimize the development of drug resistance. An ARV policy package, with five key elements similar to that adopted for tuberculosis control could provide the framework necessary for ARV delivery in sub-Saharan Africa (Table 3). One of the important activities in this ARV policy package is supervised administration of tablets (directly observed treatment—DOT) in order to ensure patient adherence to therapy. In a small impoverished community in rural Haiti, DOT-HAART as part of a package of care for a small number of patients with AIDS was shown to be effective,[30] adding support to the belief that HAART can be delivered in a setting where the general health infrastructure is weak.

A programme to deliver HAART could not be implemented nation-wide all at once. A phased approach would be necessary, the details of which need to be worked out and would no doubt vary from country to country. The general approach might be as follows. The first phase would put in place the programmatic infrastructure necessary for administration of HAART. The second phase would rigorously pilot the chosen triple-combination therapy and define simple and robust clinical management algorithms for monitoring treatment and complications, because in most districts in Africa sophisticated laboratory monitoring will not be realistic. The third phase would be to assess feasibility at district level, with the fourth and final phase being gradual country-wide expansion.

Conclusion

A meaningful challenge to the AIDS epidemic requires a huge scaling up of international support, both for ARV drugs and for basic prevention and care packages.[31] During the years 1996–1998, finance from all rich countries to sub-Saharan Africa for projects designated

as AIDS control averaged USD$69 million annually, and assuming a safe margin for under-reporting and mis-reporting total donor spending on HIV/AIDS control was perhaps twice that at most.[31] This level of funding is totally incommensurate with the severity of the AIDS epidemic. A strong case has been made for a global annual budget of $7.5 billion US in the form of grants, in order to support HAART and a package of basic prevention and care in resource-poor countries.[31] By 2005, it has been calculated that sub-Saharan Africa would need an annual expenditure of $1.5 billion US for prevention and $3 billion US for care and support, including the use of HAART.[32]

In July 2001, a Global Health Fund was established, as a source of money for the prevention, treatment and research for three of the world's biggest killers: AIDS, tuberculosis and malaria.[33] The United Nations has calculated that up to $10 billion US is needed annually to fight AIDS alone. However, at the end of the G8 Summit in the same month the fund stood at $1.3 billion US, and with other global priorities such as terrorism taking a dominant place in budgetary considerations, sufficient funds may not become available. Many countries in sub-Saharan Africa, including some of the poorest, have shown political commitment and have developed plans to scale-up treatment and prevention programmes. What they need now are resources and support from the international community.

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