Antiretroviral therapy in Africa

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We should stop and think about the risks of resistance, and ways of minimising them, before increasing access to antiretroviral therapy in Africa

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Demands for the introduction of antiretroviral therapy into Africa have been growing over the past few years. On the face of it, the availability of antiretroviral therapy at what seems to be an affordable price is good news. The treatment can produce dramatic clinical improvements in people with symptomatic HIV disease and, when used optimally, can delay the progression of disease. However, the potential short term gains from reducing individual morbidity and mortality may be far outweighed by the potential for the long term spread of drug resistance if the experience of adherence to treatment for tuberculosis is repeated. Without due forethought and planning, antiretroviral therapy is likely to be introduced to Africa in a random and haphazard way, with inconsistent prescribing practices and poor monitoring of therapy and adherence. This risks the rapid development and transmission of drug resistance.

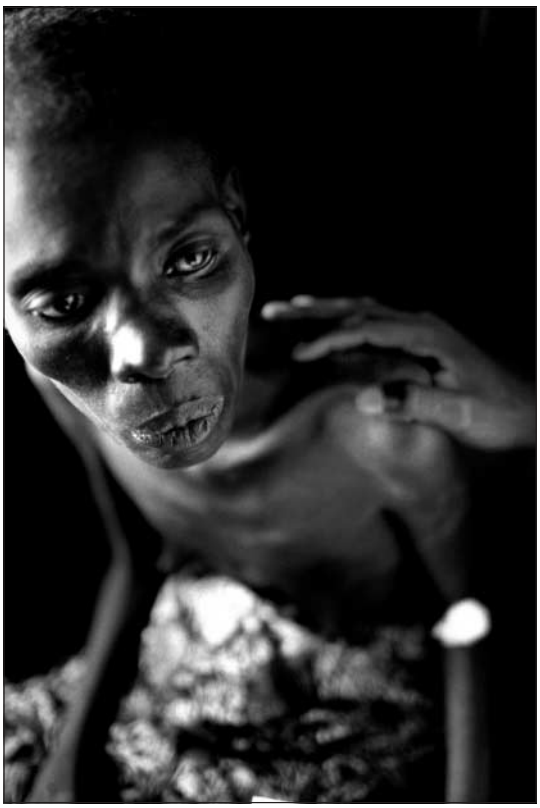
HIV drug resistance

Virus strains with reduced sensitivity to zidovudine, the first drug used to treat HIV infection, were first observed in 1989, three years after it was introduced.[1] Subsequently, resistance to every currently licensed antiretroviral drug has been observed.[2] Drug resistance within an individual patient is not confined to a single compound, and cross resistance between drugs of the same class is the rule rather than the exception.[3]

Drug resistance arises by natural selection, mutant strains being selected when the virus replicates in sub-limiting drug concentrations. The only way to prevent resistance is to use a drug regimen that reduces virus replication to virtually zero (commonly equated with a plasma virus load below 50 RNA copies/ml). In this circumstance, the probability of a mutant arising to all the drugs used in a highly active antiretroviral therapy regimen is very low. However, should the concentrations of the drugs fall sufficiently to allow appreciable virus replication, the chances of a resistant mutant being selected increase.

The concentration of antiretroviral drugs at their active site varies for several reasons including eating habits, exercise habits, and concurrent illnesses. However, the main cause of variation is the timing of the dosing schedule. Concentrations of the drug peak shortly after a dose is taken and then wane until the next dose is taken. Antiretroviral regimens are designed so that the trough concentrations of the drugs are never sufficient to allow appreciable virus replication.[4] The longer a dose is delayed, the lower the concentration falls and the more virus replication occurs. Thus, intermittent therapy and poor adherence are the principal factors leading to drug resistance. Although most resistant strains are poor at replicating and do not persist in the absence of drugs,[5] viral variants are archived as provirus in long lived memory T cells[6] and will be rapidly selected when therapy is resumed.

The only sure way to avoid the development of drug resistance is to adhere strictly to therapy. Failure to completely suppress virus replication has been shown to result in the development of resistance even at high levels of adherence (>92%).[7]



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Zambian patient in a homebased care project for AIDS sufferers

Implications of resistance

From a public health viewpoint, drug resistant strains are transmissible and pathogenic. Currently, in industrialised countries, up to 23% of incident infections are with virus strains resistant to one or more drugs.[8] The higher the incidence of infection, the more rapidly resistant variants can spread. People infected with a drug resistant virus are more likely to have their treatment regimen fail allowing the virus to develop resistance to other drugs in the combination. Good adherence to therapy, resulting in undetectable virus loads, will reduce virus transmission within the community. There is no reason to suppose that the drug resistance problems being encountered in industrial countries will not occur in developing countries.

The development of drug resistance is also of concern for the infected individual whose therapy fails as a consequence. Because of cross resistance within drug classes, people in whom the first antiretroviral therapy regimen fails often have poorer responses to subsequent regimens containing drugs of the same classes.[9 10]

In industrialised countries, therapy is routinely monitored by assaying plasma virus load.[11] This measure shows the most immediate response to changes in virus replication. Unless monitoring of virus load is adopted alongside the introduction of antiretroviral therapy in developing countries, the risks of drug resistance arising and being transmitted are greatly increased. At present, the necessary laboratory infrastructure for such monitoring is not available in most countries of sub-Saharan Africa.

Drug regimen compliance in Africa

Evidence suggests that adherence with drug treatment in Africa is low compared with that in industrialised nations. Treatment for malaria rarely exceeds three doses, yet suboptimal dosing is still seen in 60-70% of cases in Africa.[12] Treatment with antiretroviral therapy depends on long term, regular, time specific dosing, much like diabetes or tuberculosis (which is more common in Africa).

It has been suggested that giving antiviral therapy through the directly observed treatment short course (DOTS) strategy developed to monitor treatment for tuberculosis would ensure the necessary adherence. Yet, DOTS itself has met with mixed success, particularly in Africa (table). A decade after it was introduced in Africa, treatment completion rates still range from low (37%) to moderate (78%).[15] Problems that have been documented include the time and expense of travel to and from health centres, availability of drugs, and the time and costs needed to supervise treatment.[16]

Directly observed treatment for antiretroviral therapy has been tested in developed countries and met with mixed success. Estimates of average rates of non-adherence to antiretroviral therapy ranged from 50% to 70%. Adherence rates below 80% are associated with detectable virus in most patients.[7] With directly observed treatment for antiretroviral therapy still under development in industrialised nations, its introduction into a part of the world where adherence rates are generally much lower seems unconsidered. Other methods of increasing adherence to tuberculosis treatment have been suggested and tested throughout the developing world.[17] However, these have not achieved adherence greater than 70% and have not been tested on a large scale.

Success rates of directly observed treatment short course (DOTS) for tuberculosis in sub-Saharan African countries with HIV-1 prevalence over 5% (data for most recently available year, 1995-2000)[13 14]

Country	DOTS success rate (%)	HIV–1 prevalence (%)
Angola	68	5.5
Botswana	71	33.8
Burundi	74	8.3
Burkina Faso	61	6.5
Cameroon	75	11.8
Central African Republic	37	12.9
Congo	61	7.2
Ivory Coast	63	9.7
Ethiopia	76	6.4
Kenya	78	15.0
Lesotho	69	31.0
Malawi	71	15.0
Mozambique	71	13.0
Namibia	50	22.5
Nigeria	75	5.8
Sierra Leone	75	7.0
South Africa	60	20.1
Togo	76	6.0
Uganda	61	5.0
Tanzania	78	7.8
Zimbabwe	73	33.7

Excludes Zambia (21.5% HIV prevalence), Swaziland (33.4%), and Rwanda (8.9%), which did not have DOTS programmes at time of data collection.

Directly observed treatment is not the only way that antiretroviral therapy has been delivered. Nevertheless, it is the model on which most programmes are based. Studies reporting successes in delivering antiretroviral therapy in Africa have had relatively strict exclusion criteria. Study populations have tended to be urban with above average education and income, and, as such, are probably not representative of most African patients requiring treatment.[18 19] These studies are, however, a movement in the right direction as they improve our understanding of what can be achieved and what levels of infrastructure and adherence management are required.

Difficulties of antiretroviral programmes

A major problem we face in introducing antiretroviral therapy to Africa is the inadequate infrastructure to deal with the number of people infected. In developed countries the number of people likely to be poor adherers is relatively small. Treatment of this group is seen as beneficial not only to the individual but also to the wider community because it gives increased protection against spread of infection. In Africa, a higher proportion of patients are likely to fall into the category of potential poor adherers unless resource intensive adherence programmes are available.

Ideally, the way forward for antiretroviral therapy in Africa would be to introduce treatment in controlled settings. Research programmes are needed to tackle the problems of delivery and the challenges of providing the infrastructure to ensure effective access to antiretroviral therapy. We cannot afford inconsistent

Summary points

Antiretroviral therapy is becoming more affordable for developing countries

Infrastructure is also essential to deliver the complex and sensitive drug regimen

DOTS has been suggested as a method for delivering antiretroviral therapy, although it has limited success for tuberculosis in much of Africa

Suboptimal adherence to antiretroviral therapy is likely to result in the transmission of drug resistant virus strains within the community

Other methods for ensuring adherence need to be developed and evaluated

prescribing practices and poor monitoring of therapy and adherence.

A rational approach is required in which systematic delivery and proved methods for maximising adherence are as important as procuring the drugs themselves. This should be led by a respected international organisation that has the objectives of overcoming short term suffering as well as preventing a similar disaster in the long run, by insisting that antiretroviral policies incorporate a phase of piloting systems that seek to maximise adherence.

Contributors and sources: WS has worked with the World Bank in predicting the effect of HIV in West Africa, and with the Department for International Development and the London School of Hygiene and Tropical Medicine on the economics of tuberculosis control programmes. SK has worked on monitoring HIV drug resistance in trials of antiretroviral therapy conducted in the United Kingdom and Europe. TC has been in charge of the clinical services provided by the MRC unit in the Gambia since 1986 and has specialised in the care and treatment of patients infected with HIV and tuberculosis.

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Evaluating the health effects of social interventions

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Is no evidence better than any evidence when controlled studies are unethical?

Rigorous evidence on the health effects of social interventions is scarce[1 2] despite calls for more evidence from randomised studies.[3] One reason for the lack of such experimental research on social interventions may be the perception among researchers, policymakers, and others that randomised designs belong to the biomedical world and that their application to social interventions is both unethical and simplistic.[4] Applying experimental designs to social interventions may be problematic but is not always impossible and is a desirable alternative to uncontrolled experimentation.[3] However, even when randomised designs have been used to evaluate social interventions, opportunities to incorporate health measures have often been missed.[5] For example, income supplementation is thought to be a key part of reducing health inequalities,[6] but rigorous evidence to support this is lacking because most randomised controlled trials of income supplementation have not included health measures.[5] Current moves to increase uptake of benefits offer new opportunities to establish the effects of income supplements on health. In attempting to design such a study, however, we found that randomised or other controlled trials were