

PROVISION OF ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS – A REVIEW UP TO AUGUST 2003

World Health Organisation (WHO) and Department for International Development, UK

Improved prospects for expanded access to antiretroviral therapy (ART) in resource-poor settings are the result of reduced costs of antiretroviral drugs (ARVs), increased availability of cheaper generics and access to funds such as the Global Fund to Fight Acquired Immunodeficiency Syndrome (AIDS), Tuberculosis and Malaria (GFATM), private foundations, non-government organisations (NGOs), corporate initiatives, government budgets and other multilateral and bilateral donors, with the prospect of additional funding from the United States Millennium Challenge Account.

Increased affordability together with the political will has seen a rapid increase in the number of countries introducing or scaling up ART programmes.

The paper aims to elucidate the requirements for ART programmes in resource-poor settings by using existing pilot experience and lessons learnt with particular regard to:

- The feasibility of ART in resource-poor settings.
- The different approaches being taken to delivery of ART.
- The issues to be considered in scaling up ART provision.

FEASIBILITY AND IMPACT OF ART IN RESOURCE-POOR SETTINGS

Pilot studies conducted in South Africa, Uganda, Cameroon, Cote d'Ivoire, Kenya, Malawi, Senegal and India demonstrate the feasibility and effectiveness of highly active antiretroviral therapy (HAART) in a range of resource-poor settings with limited evidence of resistance. There is little evidence outside of these small studies.

Positive outcomes (good adherence, decreased viral load, increased CD4+ count, decreased opportunistic infections and side-effects) from the pilot studies compare favourably with rich countries. Patient commitment has been shown to be strengthened by careful counselling of both patients and families before commencement of therapy, ongoing support; local government and community support,

Précis by Penny Penhall.



and recovery from AIDS illnesses.

Patients on HAART do better than those who because of cost considerations are given dual nucleoside therapy. Dual therapy has limited durability and may promote more rapid emergence of drug resistance.

Effects of HAART on mortality differ. In Brazil, where there is universal access, there has been a 50% decrease in HIV-related deaths since 1996 and a median survival increase from 18 to 58 months. Improvements have been recorded at sites in most countries with the exception of the Médecins Sans Frontières (MSF) Homa Bay site in Kenya, where late presentation played a major role.

ART has decreased the risk of tuberculosis (TB) by as much as 80% in Brazil and South Africa.

In Brazil, the positive impact of HAART includes a decrease in health

service expenditure, where an estimated 358 000 hospital admissions were avoided between 1996 and 2002, saving US\$2.2 billion. Two years after introducing a comprehensive HIV/AIDS programme with ART, a Cote d'Ivoire private sector company noted a fivefold increase in company-based voluntary counselling and testing (VCT), a 94% decrease in absenteeism, an 81% decrease in HIV-related hospitalisation, a 78% decrease in new AIDS cases, and a 58% decrease in HIV-related mortality. The company saved approximately US\$750 000 in health care, funeral costs and absenteeism.

Debate on the impact of HAART on risk behaviour and implications for the spread of disease continues, but in Brazil no increase in unsafe behaviour has been reported. In Cote d'Ivoire it was found that unprotected sex was associated with *not* being on ART treatment. South Africa's Khayelitsha project confirmed this finding, with increased condom use in those on treatment.

APPROACHES TO DELIVERY OF ART

NATIONAL PLANS AND STRATEGIES

Brazil, Thailand and Botswana have national ART programmes, and Mozambique, Malawi and Kenya have developed strategic plans for scaling up (as has South Africa). Focus has differed from country to country; some have concentrated on service delivery and access to ART rather than on strategic planning, and others are reviewing their legal and policy framework.

Experience in African countries indicates that clear goal setting and integrating ART programmes into national HIV/AIDS strategic plans, with multisectoral national review, helps to define priorities for scale-up.

A review of national HIV strategic plans in five sub-Saharan countries identified a number of weaknesses in national plans and priority setting processes:

- Unrealistic resource allocation – designed for resource mobilisation.
- Priority setting by donors instead of by considerations of cost-effectiveness.
- The balance between prevention and care being determined arbitrarily.

The key issue being, *not* whether to include ART or not, but the balance between prevention and care and different care interventions.

Many large organisations suggest that HIV/AIDS programmes be included or considered in poverty reduction strategies, as they believe that addressing the epidemic is central to poverty reduction. This is not always easy in practice as organisations are not always aligned,

poverty reduction programmes do not always identify HIV/AIDS strategies, and there is concern that combining projects may distort planning and budgeting processes.

MODELS OF DELIVERY

Many countries have a wide variety of ARV providers and programmes within one country, which operate in different settings, and have different financing, logistical and clinical structures. This makes it difficult for policy makers to evaluate coverage, quality of services and equity impact.

Experience indicates that scaling up is best achieved through co-ordination and collaboration with the existing operational mix of providers, e.g. private sector (private health care facilities, private physicians, company schemes) combined with NGOs, and local and international organisations including mission hospitals, religious networks and community organisations. Systems need to be appropriate to the national context and the health system.

A literature review indicates that in most countries the public sector uses one or a combination of three models, i.e.

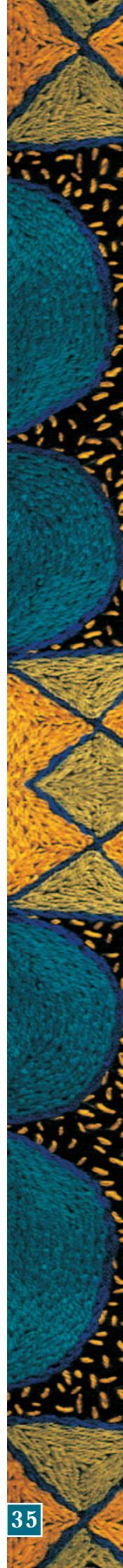
- provincial and regional hospital delivery
- district level delivery
- community clinic or community-based delivery.

PUBLIC HEALTH SECTOR

Most countries in sub-Saharan Africa are using public sector hospitals in a phased, scale-up approach beginning with selected regional or provincial hospitals, e.g. Ghana began with 2 hospitals, Botswana with 4 sites and Nigeria with 25. A number of countries use district facilities for counselling, testing, treatment of opportunistic diseases, prevention of mother-to-child-transmission (PMTCT) and monitoring and as referral points, and major public hospitals (often teaching hospitals) as the entry point for ARV treatment, e.g. Ghana, Senegal, Botswana and Nigeria. A second phase, comprising inclusion of all regional hospitals, is then undertaken. Mozambique is to make ARV available through multi-purpose Integrated Health Networks (IHNs).

NON-GOVERNMENT AND COMMUNITY ORGANISATIONS

In some countries NGOs are at the forefront of the provision of ARV treatment through pilot schemes and community programmes. A number of NGOs, e.g. MSF and AIDS Healthcare Foundation, run such pilot programmes in a number of African countries including South Africa. Faith-based networks also play a role. The number of patients treated varies from as few as 50 - 60 through to 300 or more.



Community-based organisations (CBOs) are being considered in some countries e.g. Uganda (through TASO and CDC) as a result of the successful, perhaps best-known, Haiti CBO, documented by Farmer in 2002, which provides HAART through directly observed therapy (DOT) to approximately 60 patients.

The importance of good information and adequate ART training has been shown to be essential for NGOs and CBOs.

PRIVATE SECTOR

Even in very poor countries ART has been available through the private health care sector for some time at a range of (mostly) high prices. High prices are not a guarantee of quality, as doctors sometimes prescribe according to patient affordability and local availability of ARVs. Some studies have shown that prescribing is consistent with international standards and others that drug regimens and frequency of monitoring are sub-standard. Concerns include monotherapy, resistance development, poor adherence, and unreliable drug supply leading to intermittent treatment and regimen switching.

Multinationals providing ARVs to their staff include soft-drinks manufacturers (Coca-Cola), breweries (Heineken), car manufacturers (Daimler Chrysler, Ford) and mining companies in Botswana and South Africa (e.g. Anglo American). Electricity companies in South Africa (Eskom) and Cote d'Ivoire also provide ART.

Some evidence from Africa suggests a cost saving for companies providing ARV, although studies suggest that affordability is more important than cost saving in influencing the initiation of the provision of ART.

A trend towards shifting the burden to households and to government through cost-sharing models including pre-employment screening and restructuring of employee benefits, has been identified.

ISSUES IN SCALING UP ART PROVISION

SELECTION OF BENEFICIARIES

Coverage

In December 2002, the World Health Organisation (WHO) estimated that < 1 in 18 people in middle- and low-income countries, thought to be in need of ART, were on treatment. Nearly two-thirds of these were in Latin America and the Caribbean. In sub-Saharan Africa, only 50 000 of 4.1 million needing ART were on treatment.

Eligibility criteria

WHO guidelines for resource-poor settings recommend

treatment for the following categories of HIV-positive people:

- diagnosed with AIDS
- with a CD4+ count of < 200/ μ l, or fulfilling the guidelines based on clinical diagnosis where CD4+ testing is not available. In countries with inadequate resources to treat all people requiring ART, additional criteria are required in the decision-making process.

Clearly defined economic, social and biomedical criteria are required to determine eligibility for free treatment to ensure equitable access. Communities need to be made aware of these criteria. MSF in South Africa has established clear criteria which include living in the geographical catchment area, number of dependants, health status, income, disclosure and activism.

Equity and priority target groups

Scale-up programmes should be informed by equity issues and consideration given to the poor, different geographical regions, rural v. urban populations, specific population groups, gender and children. Socio-economic determinants for free and subsidised ARVs need to be carefully defined to ensure equitable access. Experience has shown that many of the poor may not be able to afford ART even if it is heavily subsidised as the lowest cost of triple therapy can be as much as twice the average monthly formal sector wage, e.g. in Mozambique. In cost sharing systems, levels of charging, means testing and waiver systems need to be addressed.

Countries' objectives differ. Some aim to achieve the widest possible geographical coverage while others target key groups which vary by country, e.g. HIV-positive people with serious immune system damage, continued treatment of HIV-positive mothers identified in PMTCT strategies and their male partners, post-exposure prophylaxis (PEP) for health care workers, patients with TB, and victims of sexual assault.

Inclusion and free access criteria need to be flexible and evolve in accordance with changes in drug prices, availability and financial resources.

HEALTH SYSTEMS

Systems strengthening

There is limited information on the impact of HIV/AIDS on already constrained health systems of developing countries. Scaling up has the potential to strengthen systems and improve outcomes for non-HIV-related conditions if investment is used to address infrastructure, human resources and logistical weaknesses, e.g. in Thailand. Improving clinical services can boost staff morale, e.g. in Haiti. Conversely ART programmes could

weaken poor health systems without appropriate investment in systems strengthening. Situational assessments of regional and district facilities to identify needs and gaps and system strengthening requirements have been undertaken by certain countries, e.g. Kenya.

Integration of services

It is generally accepted that ART needs to be delivered as part of a comprehensive approach to prevention, care and support services including voluntary counselling and testing (VCT), PMTCT, diagnosis and treatment of opportunistic infections (OIs) and other HIV-related illnesses. Integration and co-ordination of services is advised by WHO as opposed to setting up new parallel structures. Lower levels of the system can act as entry points to regional treatment centres offering ART, or VCT and TB programmes can act as entry points.

Infrastructure

Limited infrastructure is a major constraint to scaling up of ART. There is a lack of clarity regarding the minimum infrastructure requirement, its costs and efficiencies of scale. Laboratory, pharmacy and clinical facilities are required for successful ART delivery.

Kenya is one of the few countries to have conducted a comprehensive situational assessment of public health facilities.

Human resources

Staff shortages are a major constraint to scaling up and in many of the worst-affected countries the health sector is facing a crisis in skilled human resources due to migration to the private sector and other countries and exacerbated by HIV/AIDS-related attrition.

Innovative ways to address lack of human capacity include lay counsellors, reduced frequency of visits for stable and adherent patients, prescribing of ARVs by district hospitals but collection of drugs and monitoring at satellite health centres using simplified clinical review guidelines and simple but effective record keeping and drug monitoring systems.

Training for clusters of doctors, nurses and other health care workers is critical, as is a common approach and message. Training strategies and methods need rethinking in order to incorporate responsive continued education given the rapidly evolving nature of ART.

Improved staff management (capacity to co-ordinate, supervise and monitor the scaling up process at all levels) would substantially increase staff productivity within the broader contexts of decentralisation and health sector reform.

Drugs and supplies

Effective ART programmes require regular and timely supplies of competitively priced quality drugs, laboratory reagents and related supplies, and drugs for OIs. This requires buffering against uncertainties in funding to minimise risks of interrupted supplies and prevent resistance.

Countries planning a scale-up need clear drug procurement, storage and distribution policies to prevent misuse. Secure supply chains and storage systems need strict monitoring to prevent leakage from public programmes.

Some drug registration processes may be slow and complex and procurement hampered by lack of drug information and corruption. Import taxes and duties add to the cost of ARVs and reagents, so local production (as in Brazil, India, Thailand, China) and the use of generics (Kenya, Mozambique, South Africa, Ethiopia and Ghana) are preferred options.

Assessment of challenges

Recent research has identified the following challenges in countries wishing to scale up ART: weak public sector management of essential drugs, poor storage facilities, weak transportation systems, problematic customs processes, diversion of products, inadequate training, lack of information systems, inaccurate quantification and forecasting (often based on consumption rather than morbidity data). The trend towards decentralisation requires support for district level planning and informed decision-making and drug budgeting.

Key logistics management issues

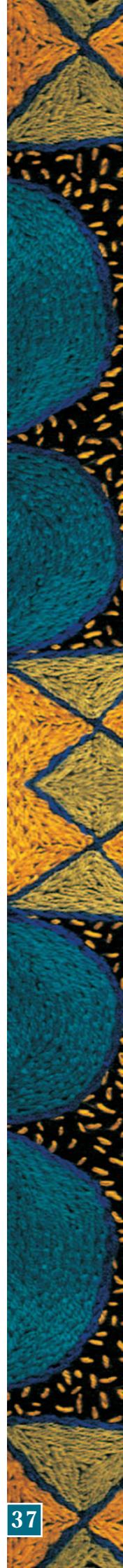
Key management issues listed by WHO/UNAIDS include the role of public v. private sector, supportive policies and legal environment, harmonised or standardised procurement, quality assurance and control, criteria for quantification and forecasting, standard treatment guidelines and inclusion in essential drug lists (EDLs), inventory control systems, secure transportation and storage, monitoring of prescribing patterns, dispensing patterns and stock levels.

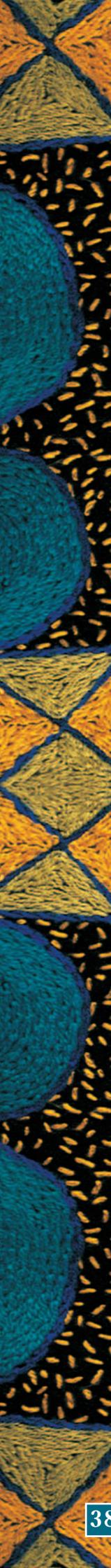
Logistics management information systems need to be user-friendly and a minimal burden to health workers, to provide timely data, and to respond flexibly to consumption and regimen changes and drug substitution.

CLINICAL MANAGEMENT

Standard guidelines

Guidelines reduce treatment complexity and the cost of treatment and monitoring, and increase access to ART,





especially in resource-poor countries. In addition, local guidelines simplify eligibility criteria for initiating therapy and standardise first- and second-line therapy.

Some research in Zambia and Mexico indicates that lack of enforcement of guidelines, cost of triple therapy, and poor training of prescribers can lead to poor prescribing habits.

Alternative treatment regimens

Despite price decreases, HAART remains expensive relative to many other treatment modalities and remains complex in spite of the introduction of treatment regimens.

Simpler and more affordable regimens are being sought and studied, including structured treatment interruption, which appears the most promising option at present.

Clinical and laboratory monitoring

Laboratory monitoring is essential for the accurate assessment of the outcomes of ART and requires adequate facilities and well-trained staff to conduct accurate CD4+, viral load, and basic safety tests for side-effects. In most resource-poor countries laboratory services require strengthening.

While the price of ART has decreased, the price of tests has not (though in South Africa there have been reductions). Reduced prices for tests and reagents need to be negotiated, cheaper generic alternatives sourced, and new technologies and assays developed. Simplified and less frequent monitoring methods (e.g. one CD4+ every 6 months) and the use of low-cost alternatives to CD4+ tests are being studied. These require more reliance on clinical markers such as weight and early detection of any deterioration in health, e.g. OIs. It has been suggested that viral load testing be confined to monitoring of resistance at national referral centres.

Alternatives to the present CD4+ testing methods include dynabeads and cytospheres (counts measured by flow cytometry and non-flow cytometry), but their disadvantages include being labour intensive and requiring trained technicians, limiting the number that can be processed per day. The WHO recommends further studies before any recommendations are made for developing countries. Alternatives to polymerase chain reaction (PCR)-based and bDNA-based viral load assays are also being evaluated.

Drug resistance

The development of drug resistance is a commonly cited concern regarding rapid scale-up programmes in resource-poor settings, although a World Bank meeting in June 2003 concluded that there was no empirical evidence that it is more problematic in developing countries than developed

countries. They concluded that concerns should not delay programmes but recommended the promotion of rational drug use and good patient adherence.

Most developing countries cannot afford resistance testing for individual patients and most laboratories are not equipped to perform resistance tests. The WHO and various partners are working towards a global HIV drug resistance surveillance programme to record prevalence, identify contributory factors and strategise to minimise and limit the spread of resistant organisms.

DEMAND AND ADHERENCE

Uptake of ART

Availability and lowered cost of ART does not guarantee access, as uptake is influenced by financial, organisational, physical and social factors.

As many people are unaware of their HIV status, providing and improving access to VCT is an initial and vital step in increasing uptake. A study conducted in Kampala, Uganda, found that despite decreased ARV prices, uptake did not increase because of the limited knowledge and negative attitudes to ARVs of health care workers and patients. Subsequent training of health care workers and the use of people taking ARVs to educate others increased the number of patients. ARV availability and usage in PMTCT programmes has increased uptake of VCT in certain settings such as South Africa and Haiti.

The provision of free-of-charge diagnosis, drugs and monitoring improves uptake, although payment for OIs may remain an obstacle. Where patient co-payments are required, assessments on willingness to pay, ability to pay and impact of payments on households should be undertaken. In households in which more than one person is infected, cost is even more problematical.

People with private health insurance may not wish to claim for reimbursement due to fear of disclosure and discrimination.

Barriers to access include lack of transport, fear of disclosure, stigma and discrimination. There is however evidence that ART availability increases uptake of services, changes community perceptions of AIDS and reduces discrimination.

Community education is essential in improving uptake and successful implementation of programmes.

Adherence

Concerns regarding patient adherence to ART in resource-poor settings have been proved unfounded, programmes such as the MSF pilot programme in Khayelitsha, South

Africa, having demonstrated adherence of > 95% after 3 months of treatment. The programme combines patient-centred education with individual, peer and practical support.

Brazil attributes high rates of adherence to affordability, fixed-dose combinations, community participation, involvement of civil society organisations and adherence-support groups and support houses.

Other factors promoting adherence include affordability, disclosure of status to partners and family and regimens with limited numbers of pills. Poor clinical management and side-effects can adversely affect adherence.

More research is required and a study to identify the main determinants of adherence, barriers to adherence and the identification of effective interventions, is being undertaken in Mombasa, Kenya.

Community involvement

Experience indicates that uptake and adherence are improved in communities that have been adequately prepared for scaling-up programmes (highlighted at a WHO/UNAIDS meeting recently). Planning and budgeting for health care provider training and capacity building in communities is critical to the success and sustainability of expanded ART programmes.

In Brazil and South Africa civil society organisations have played a key role in advocacy and community mobilisation, e.g. the Treatment Action Campaign. In countries in which ART is not universally available, community involvement is becoming increasingly important in ensuring that decisions are made in a transparent and equitable manner.

AFFORDABILITY AND FINANCING

ARV prices

Increased competition and generics have substantially decreased ARV prices, enabling more governments to provide ART through the public sector. In May 2003 the least expensive *brand name* combination recommended by the WHO for low-income countries cost approximately US\$675 per person per year and the least expensive *generic* combination just under US\$300 per person per year.

In resource-poor countries, local manufacture and imported generics from Brazil, India and Thailand have made significant contributions to increased affordability.

Costing and sustainability

Developing countries with a high HIV incidence face or anticipate considerable difficulties regarding cost of public

programmes. Most governments will continue to require external aid to provide free or highly subsidised ART for some time to come. Only 7 of 19 Accelerating Access Initiative (AAI) countries have been able to fully subsidise ARV therapy.

Geffen *et al.* recently reported that a fully comprehensive HIV/AIDS response was feasible in South Africa, including ARV drugs, training and improvement in infrastructure (subsequently the price of ARVs has decreased and locally produced generics are soon to be made available). There is significant potential for ARV costs to be offset by reductions in hospitalisation and treatment of OIs (US\$400 million in 2001 – National Treasury of the Republic of SA, 2001).

Financing mechanisms

Long-term funding of programmes through the public sector is unrealistic in most resource-poor countries and multi-funding approaches are needed. A range of such strategies include drug and laboratory cost reduction, graduated cost sharing with the assistance of NGOs and private sector enterprises (based on ability to pay), national government exchequer funds, employer treatment schemes, health insurance scheme coverage of ART, social insurance funds, and donor support.

MONITORING AND EVALUATION

ART programme monitoring and evaluation (M&E)

M&E will assist in the identification of challenges and speed up the application of lessons learned. They need to identify inefficiencies, obstacles and adverse effects and address feasibility and cost issues and consider ART within the context of comprehensive care. In addition to clinical outcomes M&E will need to include equity, quality of care, and impact on risk behaviour issues.

Methods of patient and drug monitoring differ by country but include paper-based identity or photo cards, health facility registers, smart cards, finger-print readers, bar-coded drug packaging and electronic databases and sophisticated computer technology and fixed and mobile telephone-based links to central monitoring points.

Journal 15 will contain a précis of the 'Review of Experience' section of the original report prepared by the Health Systems Resource Centre for the UK Department for International Development in collaboration with the World Health Organisation.

