CENTRE FOR SEXUAL & REPRODUCTIVE HEALTH

PROVISION OF ANTI-RETROVIRAL THERAPY FOR PEOPLE WITH HIV/AIDS IN DEVELOPING COUNTRIES

REPORT

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List of Acronyms and Abbreviations

ART	Anti-retroviral therapy
ARV	Anti-retroviral
CBOs	Community Based Organisations
DAI	Drug Access Initiative
DART	Developments of ART
DOTS	Directly Observed Treatment Schedule
FDA	Food & Drug Administration
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency virus
HIVNAT	HIV Netherlands, Australia, Thailand
IAPAC	International Association of Physicians in AIDS Care
JCRC	Joint Clinical Research Centre
LDC	Least Developed Country
LSTM	Liverpool School of Tropical Medicine
MDR TB	Multiple Drug Resistance TB
MoH	Ministry of Health
MRC	Medical Research Council
MTCT	Mother to Child Transmission
NGO	Non-Governmental Organisation
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
PI	Protease Inhibitors
PWA	People with AIDS
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TASO	The AIDS Support Organisation, Uganda
UNAIDS	United Nations Joint Programme on AIDS
VCT	voluntary counselling and testing
VCT	Voluntary Counseling & Testing

1. Background/Context

1.1 The HIV/AIDS epidemic has shattered the comfortable dichotomy between tropical and temperate medicine. For the first time in generations, a major public health problem and treatable disease is a top priority in both resource rich and resource poor countries. The huge disparities in the responses generated - dictated by resource availability rather than need - is highlighted by differences in care, especially ART.

1.2 Up till now, the main thrust of development/health assistance has been in HIV/STI control. This is clearly identified as a public good and is highly cost-effective. After STI services are strengthened and condoms are distributed what are the next targets? Critical in this is sustained behaviour change but this requires a more mainstreamed approach that properly includes provision of services for those infected.

1.3 The HIV epidemic is a great threat to development. How a problem is defined determines what will be done about it. It is increasingly short-sighted just to see HIV as an STI within reproductive health. A broader definition and approach is needed within the health sector; and beyond health, which can help to inform and promote inter-sectoral policies on HIV/AIDS. This definition will need to include HIV as a disease as well as a problem just to be prevented. Access to ART is at present the dominant care issue.

1.4 Different classes of ARV drugs exist and there are several proprietary preparations in each (see Appendix 1). These should be used in combination and may be toxic. ART is very complex and specialist training is required to administer it. Monitoring usually relies on sophisticated laboratory services, which are expensive and only available in a few (private-for-profit or research) settings in large cities in resource-poor countries.

1.5 The five main manufacturers of antiretroviral (ARV) drugs recently announced unprecedented cost slashing of proprietary drugs for resource-poor countries.To date no prices have been announced but the discount is likely to be as much as 90% of current US or European price; and far below (>50%) the current discounted prices negotiated by UNAIDS for the pilot Drug Access Initiative. However, these proposed price cuts are based on several conditions, including certain government commitments and health service capacity, which make it unlikely that cheaper drugs will be available in the near future.

2. Current prevalence of art in resource-poor settings

2.1 There appears to be no national statistics from any low-income country that report on importation of individual drugs used in ART. Such figures would probably be unreliable, reporting licensed proprietary drugs imported through legitimate channels rather than generic drugs - produced illegitimately in India and Thailand. Importation gives no handle on how drugs are prescribed. Counterfeiting is allegedly occurring.

2.2 The Ugandan UNAIDS drug access initiative monitors how many clients are using discounted ART on a relatively regular basis. The most recent report identified about 900 patients (approx 0.1% PWAs)

2.3 Informal links between NGOs and PWA/patient support groups, and with relatives (e.g. in UK), in the North ensure the (erratic) supply of issued/prescribed but unused or even time-expired drugs.

2.4 It is believed (no data exist) that many desperate PWAs at some stage buy ARVs or traditional/quack medicines in the search for a cure. Knowledge is extremely limited (see 10.2). Invariably improperly used, the risks of ART are enhanced (Section 3); and significant income/reserves will have been wasted.

2.5 In middle-income countries of Latin America, ART is widely accessible, financed by insurance or the state. In Thailand, with generic ARV production, it is assumed that ART is being widely promoted.

3. The risks associated with ART

3.1 Drugs are potentially toxic for the individual. Few data exist on incidence or relative importance.

3.2 Improper use (by physician unfamiliar with ART; by patient who poorly adheres because of toxicity or ability to pay) is a grave threat in the promotion then spread of HIV drug resistance. HIV is particularly prone to develop resistance mutations to some agents – in particular nevirapine. (*cf* MTCT).

3.3 All cost analyses conducted in LDCs assume fully sensitive HIV infection with predictable response to ART. Widespread resistance will complicate ART and undoubtedly increase costs (*cf* MDR TB)

4. Relative priority of secondary/tertiary HIV prevention vis a vis other health concerns

4.1 It is important to note that provision of specialist HIV/AIDS services, which includes ART, is the highest level of HIV care services when these are laid out in a hierarchical fashion (Appendix 2). It makes little sense to concentrate on the higher levels without the basics. Politically, ART is symbolising care.

4.2 ART effectively reduces plasma viral levels and this will translate into reduced transmission of HIV sexually as well as vertically. It is unclear how much secondary prevention comes from ART. Viral load reduction depends on what combination regimen is used; HAART/triple therapy is most effective but dual therapy also reduces viral load (appendix 1). No modelling has been done and no cost-effectiveness data or DALY figures have been generated for ART in resource-poor settings to date. Of concern, there are data from the US that suggest safer sexual behaviour is reduced in people taking ART.

4.3 Additional tertiary benefits include the effects of voluntary counselling and testing (VCT) that needs to be implemented to identify clients for ART. It is well documented that with good

counselling, knowing HIV status is a powerful incentive to behaviour change for both HIV-infected and uninfected.

4.4 A recent population projection model for S. Africa (Wood et al Lancet 2000: **355;**2095-2100) noted that triple therapy for 25% of HIV-infected adults would prevent a 3.1 year decline in life expectancy that was sustained; and avert more than 430,000 incident AIDS cases. Neither secondary nor tertiary effects on transmission were modelled. The intervention would consume 12.5% of health-care expenditure.

4.5 Influential publications (Confronting AIDS; World Bank 1997) conclude that ART is not a public good because of the overwhelming number of more cost-effective health priorities. Recent price shifts and modelling exercises as in 4.4 are beginning to challenge these conclusions. Moreover, the political environment in several countries seems to be moving, prioritising care (thus ART) more prominently.

5. Interventions currently being pursued; roles of bilaterals and multilaterals

5.1 UNAIDS co-ordinates a four-country (pilot) HIV/AIDS drug access initiative (DAI). This focuses on drugs for opportunistic infections as well as ART, though most activity has been with ART. The idea is preferential, not subsidised drug pricing negotiated with industry, delivered by approved centres for whom guidelines and training is provided. Cost is the main barrier to uptake (see 2.2) and will remain so even with massive price cuts unless/until ART is highly subsidised. Equity is a secondary issue as there are few centres (all in the cities) with the capacity and infrastructure to implement the initiative.

5.2 A consortium of researchers (Gilks, LSTM lead investigator) is poised to evaluate Developments of ART (DART) appropriate for Uganda (pulse therapy or structured treatment interruptions where regular drug-free periods are taken) and Hydroxyurea a potentially valuable but toxic immuno-modulator. The study site is the MRC/DFID AIDS in Uganda Programme, in partnership with TASO. MRC are likely to fund the study (banded alpha+) because of its strategic importance but drug-company support is a pre-requisite for this. A secondary benefit if funded will be the development of a Ugandan trial centre.

5.3 Similar (smaller) ART studies focussing on local issues are underway through the HIVNAT collaboration in Bangkok (Netherlands, Lange; Australia, Cooper; Thailand, Phanupak) in existence since 1998. A secondary benefit is the development of a Thai trials centre, independent of industry.

5.4 Few other interventions in adult therapy are underway to our knowledge. Uncertainty of public good, affordability and strategic relevance/priority are widespread. The field is however fast moving (*cf* major drug discounting). Increasing attention in MTCT trials is focussed on the need to offer therapy to the mother after delivery and perhaps also the child, as this is standard of care in Industrialised countries.

6. Likely impact of greater ART access on views about ART for wider populations

6.1 The prevailing view is that, except for MTCT, ART is not a public good (see 4.5). How the political climate will change, and the consequences for government policy in individual countries is difficult to predict. If ART is shown to be beneficial, and an intervention that richer members of society are prepared to purchase for themselves from private-for-profit providers then governments are unlikely to step in and suddenly want to subsidise this (except perhaps in francophone Africa for the elite). If ART is shown to be widely abused (see 3.2) then governments may be forced to introduce some sort of regulation to guard against HIV drug resistance, although this could be difficult.

6.2 Private use will be highly price sensitive but will always exclude the poor. Donors may wish to support ART for poor people because of equity, though it is likely to continue to be seen as a low priority by most bilaterals. There may be some argument for supporting ART because of secondary benefits on HIV transmission (see section 4) but if adverse impacts on sexual behaviour are seen, this is unlikely.

7. The main issues raised by HIV/AIDS civil society groups and health advocates

7.1 Equity of access to care is the main argument used by AIDS activists in the West. There is a certain zeal to these advocates who have just "discovered" the huge gaps between developed and developing countries (see 1.1). There is little in the way of structured argument including cost-effectiveness, capacity to implement, financing or prioritisation in the approach of most activists. HIV/AIDS is not just one of many priority issues, it is the only issue that counts. This can make dialogue with them frustrating. Particularly challenging groups here include the French activists in Act-up Paris.

7.2 There is far less of an outcry from low-income countries. Few activists are very vocal or visible; most are pragmatic - there appears to be more acceptance of the power of money to purchase advantage including health. With a more normalised approach activist groups may become far more vocal.

7.3 These arguments are translated into viewing the pharmaceutical industry as a profit-driven monster accountable only to shareholders with no morality or concern to act on the obvious inequity. Whilst naïve, emotional pressure on companies can secure major results in drug pricing (cf 1.5; and the announcement by Pfizer in early 2000 following Act-up pressure in the US that it was to offer to donate fluconazole to South Africa to treat cryptococcal meningitis[1]. Fluconazole is soon out of patent; and cheap Thai generics are available).

[1] This offer has recently been rejected by the South African Government

7.4 The second issue is the obvious fact that HIV is very much a developing country epidemic now with most of the burden falling on those countries and communities least able to cope. Increasingly the impact on life expectancy and development is also being referred to. Working with NGOs, CBOs, and care groups in a responsible way is led by IAPAC (see section 9).

8. The lobbying and market strategies of the International Pharmaceutical Industry

8.1 Industry is very aware of the access to ART debate. Slashing drug prices for resource-poor countries is a significant step, although prices probably remain above production costs. Cynics argue this is partly motivated by an attempt to preserve brand name and image in the face of cheap generic imports (cf Pfizer and fluconazole see 7.3). ART is highly price sensitive and use will undoubtedly rise when massive discounting eventually hits the marketplace. The risks discussed in section 3 will be very real. Private health care delivery is not supervised and the health market is universally poor at regulating itself.

8.2 Bristol Myers Squibb announced in 1999 a substantial ($100m) initiative in southern Africa "Secure the future" (managed by Jim Sapirstein). The political problems around ART and the cause of AIDS in South Africa have generated several problems for the initiative and it has had to date a relatively low profile.

8.3 In the past, Pharmaceutical companies have invested in small-scale trials of specific ARVs in low-income countries, often to generate safety and tolerability data for FDA licencing. There may also have been in the past the desire to show activity in Africa to concerned shareholders.

9. Key players in the field

<u>UNAIDS and the Drug Access Initiative (DAI)</u>

Badara Samb; Policy, Strategy and Research (PSR), UNAIDS
Jos Perriens, PSR, UNAIDS
Dorothy Ochola, DAI coordinator, MoH Uganda

<u>NGOs and activist groups:</u>

Jose Zuniga, Director International Association of Physicians in AIDS Care (IAPAC)
Marie de Cenival, Act-up Paris
There are many small PWA groups in Africa but few are really key players yet

<u>Knowledge Generation and Research:</u>

Janet Darbyshire and Ab Babiker, MRC clinical trials unit
Steven Forsythe, Charles Gilks, LSTM
David Cooper, NCHECR, New South Wales Australia and former IAS chair
Peter Mujenyi, Dorector JCRC, Kampala

<u>Pharmaceutical Industry:</u>

Jim Sapirstein; BMS and Secure the Future
Dorothy Bray; Glaxo Wellcome
Brian Elliot, Joseph Saba, Axios (independent consultants to industry)

10. Minimum systems requirements to make interventions feasible for wider replication

10.1 Trained and knowledgeable health professionals are critical for the safe and effective use of ART. Few centres exist in Africa where such training could be offered (JCRC, Kampala; several in S. Africa). Ideally clinical guidelines should be developed based on local evidence and efficacy results.

10.2 Education and information for patients as purchasers of ART is very important. At present it is assumed that with desperate patients who have little or no knowledge of what to expect that sub-standard
care and even fraudulant practice is widespread. Demand for "quack" medicine or traditional cures is widespread and is equally impoverishing to households and should be a target for information as well.

10.3 The laboratory services required for monitoring ART toxicity and tolerability, and for evaluating clinical progress are well rehearsed in several publications (eg Guidance modules on ART, nunber 5).

10.4 Improved capacity (extra staff and clinic space for privacy) for VCT. VCT is the entry point to any care initiative. DFID-funded studies in Kenya (HAPAC, Arthur/Forsythe/Gilks) show how rapid testing can be implemented at health centres. Any service delivering ART will be new, be very labour intensive and will require extra trained staff and space for it to be set up then run efficiently and effectively.

10.5 Regional clinical trial centres need to be supported and developed, which will have the expertise and capacity to ask questions about new ARV drugs and ART combinations relevant for local settings. This is accepted with HIV vaccine trial centres by many organisations.

11. Gaps in the field – current knowledge or intervention

11.1 It is generally assumed that treatment regimes developed for the US/Europe and standard of care will be used in resource-poor settings. There is however a need to evaluate regimens that may be more suitable where resources are limited (eg older generation dual therapy, cheaper but less effective; see 5.2).

11.2 Studies to examine/model the secondary and tertiary benefits/impacts of ART on HIV transmission.

11.3 Innovative ways of working in effective partnership with the private-for profit sector need to be explored and evaluated (training, guidelines, supervision, a system of accreditation)

11.4 IEC material and strategies for likely users or purchasers. Realistic expectations must be generated: No cure, some benefit but at a significant cost, access through a trained physician and

a proper clinic.

Appendix 1: Antiretroviral drugs and notes on combination therapy

Generic Name	Proprietary or Brand Name	Drug Class	Daily Dose 70kg adult	Cost in US$ for 3 Months
Abacavir (ABC)	Ziagen	NRTI	600 mg	950-1200
Didanosine (ddI)	Videx	NRTI	250 mg	420-700
Lamivudine (3TC)	Epivir	NRTI	300 mg	690
Stavudine (d4T)	Zerit	NRTI	60 mg	700-730
Zalcitabine (ddC)	Hivid	NRTI	2.25 mg	630
Zidovudine (AZT)	Retrovir	NRTI	600 mg	720-860
AZT plus 3TC	Combivir	NRTI	600 + 300	600-1300
Indinavir	Crixivan	PI	2400 mg	1350
Nelfinavir	Viracept	PI	2250 mg	1670
Ritonavir	Norvir	PI	1200 mg	2080
Saquinavir	Invirase	PI	600 mg	1720
Efavirenz	Sustiva	NNRTI	600 mg	1025
Nevirapine	Viramune	NNRTI	200 mg	740
Hydroxyurea	Hydrea	Modulator	1000 mg	16

Brand/proprietary names may differ in different countries; generic names or initials do not.
Costs are for single drug in standard dose for three months. These are NOT the discounted prices.

Notes:

A. Three classes of drug are licensed and widely used. These are the nucleoside reverse transcriptase inhibitors (NRTI), the first effective anti-AIDS drugs which inhibit DNA being formed from viral RNA (reverse transcription). Non-nucleoside reverse transcriptase inhibitors (NNRTI) inhibit the same enzyme but in a different fashion and thus enhance NRTIs. Protease Inhibitors (PI) inhibit viral assembly. Hydroxyurea is believed to be an effective modulator and it is very cheap; widely used in Africa. No evidence exists on efficacy or toxicity (*cf DART study in Uganda see section 5.2).*

B. As with anti-tuberculosis therapy, prolonged single drug therapy should be avoided as it is will inevitably with time generate drug-resistant mutants. This can happen very quickly over a few weeks with some Pis and NNRTIs (including Nevirapine). Drug resistance is usually broad and across the class of drug, though there is especially with the NRTIs considerable heterogeneity.

C. Current standard of care involves three drugs from at least two different classes. The so-called Highly Active Antiretroviral Therapy (HAART) has superseded dual NRTI therapy, which was the standard of care in the West before the development of PI class of drug. Dual therapy may have a role to play in improving quality of life and survival - at less cost thus with wider access. Some consider that only the best standard of care should be used and it is unethical to prescribe "sub-standard" care.

D. Considerable expertise is needed to prescribe these drugs in combination properly. Some combinations are ineffective, while some potentiate toxicity. Monotherapy must be avoided. With no supervision, little or no training but widespread demand for drug there is much illegitimate prescribing and use which exacerbates the emergence of drug resistance. Therapy for drug resistant infection is (again like multi-drug resistant TB) very complex and can be very expensive.

E. Monitoring is needed for side-effects and toxicity. Progress is judged clinically and also by expensive markers of disease progression which include CD4 count (@$15) and viral load measurment (@$60-80). Access to quality-controlled and reliable laboratory facilities is at present very limited in most regions.

F. Adherence to therapy is increasingly recognised as a problem in the west, especially to the more complex triple drug regimens.

Appendix 2: A heirarchy of different care levels for resource-poor countries

Care level	Services	Comments
The Essential Minimum *To be able to deliver any form of HIV/AIDS care and support, a certain minimum level of specific services needs to be provided.*	Universally accessible HIV testing Support and counselling for the person with HIV/AIDS Information and education which includes clear prognosis and advice on care and support issues Access to PWHIV/AIDS groups	Most countries in Africa have started implementing these basic minimum essential services. Once implemented, providing basic HIV/AIDS education and information, and training staff in counselling and support skills, is relatively cheap and sustainable.
Basic care delivery within the existing health-care services *Most HIV/AIDS clinical care in Africa is delivered by the existing health services, which are under increasing pressure as demand grows. Extra capacity must be developed; if not services will deteriorate or collapse and the whole community will suffer.*	Restructured Tuberculosis control services with the capacity to cope with rising demand Restructured hospital services with the capacity to cope with rising and changing case-load in equitable fashion (HIV/AIDS and non-HIV equally considered) Improved primary health care services (health centres, clinics and dispensaries) to include specific HIV/AIDS care packages More resources for terminal care	DOTS is being introduced and will improve the capacity for TB control to be delivered. Where confidence exists in hospital care, crowding out of patients and reduced quality of services are becoming evident. No solutions are yet identified. Often spare capacity in clinics and health centres; little yet done to develop existing potential or improve referral patterns.
Introducing specific HIV/AIDS clinical services *It will usually be appropriate to set up specific (new) HIV/AIDS clinical services only if basic level services are in place, and the existing health services are delivering effective basic care*	The purchase and provision of drugs for opportunistic infections that are not on essential drugs list Establishment of technology to diagnose and manage common opportunistic infections Provision of clinics and centres from where primary/secondary prophylaxis can be delivered	To pay for such services, more money has to be voted to the Health Sector or redistributed within existing Health budget For many African countries the initial stumbling block has been the treatment of fungal infection Equity and access issues complex and largely unresloved
Providing disease-modifying anti-retroviral therapy *At present this is very expensive to implement; it is likely to be more cost-effective to increase life-span in Africa by reducing the incidence and improving outcome of specific HIV/AIDS infections, particularly TB.*	The purchase and provision of antiretroviral drugs in keeping with current consensus guidelines Establishment of technology to manage HIV/AIDS patients on antiretroviral therapy Expansion of existing HIV/AIDS treatment clinics to accommodate	Massive investment necessary to finance such a new initiative, and sustain it once implemented If poorly implemented threat of drug-resistance is major concern Equity and access issues complex and largely unexplored

	antiretroviral therapy	

Appendix 3: Core reading and source material

The implications of antiretroviral treatments: informal consultation 1997. WHO/ASD/97.2

The consultation was called in response to recent developments in ART announced when the first impact of HAART was appreciated in the west. It discusses and summarizes the essential points made during the presentations. The case presentations are interesting and broad. Although held in 1997 almost all the issues are still highly relevant.

Guidance modules on antiretroviral treatments. WHO/ASD/98.1 and UNAIDS/98.7

This set of 9 modules provides expert guidance on many of the complex issues surrounding decisions to introduce ART in resource-poor settings. Included are modules on

1. Introduction to ART
2. Introducing ARTs into health systems; economic considerations
3. Planning and integration into health systems
4. Safe and effective use of ARVs
5. Laboratory requirements
6. MTCT
7. Post-exposure prophylaxis
8. Regulation, distribution and control of ARVs
9. Ethical and societal issues

Background

- *Confronting AIDS. Public priorities in a global epidemic* World bank/OUP 1997
- *Care and support for people with HIV/AIDS in resource-poor settings* DFID Health and Population occasional paper; Liverpool School of Tropical Medicine 1998