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Guidance Modules on Antiretroviral Treatments

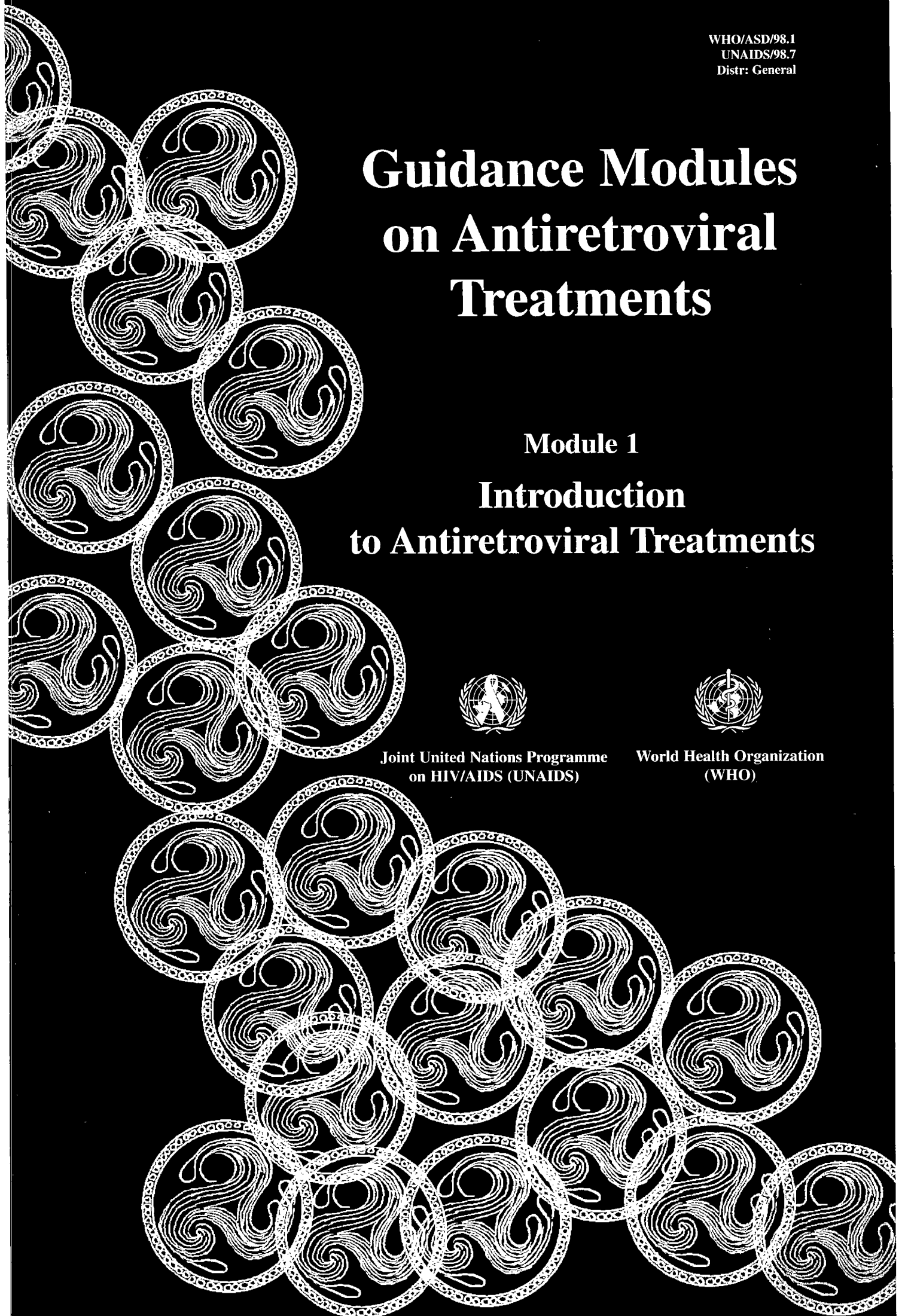
Module 1 Introduction to Antiretroviral Treatments



Joint United Nations Programme
on HIV/AIDS (UNAIDS)



World Health Organization
(WHO)



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Module 1

Introduction to Antiretroviral Treatments

HIV/AIDS and ARVs in developing countries: the reality

John found out he was HIV positive in 1989 when he was offered a place at university in the USA. A requirement before taking up his place was a medical examination which included an HIV test. He was devastated when the positive result came back as he not only lost the opportunity of studying abroad but he also had to face the knowledge that he had a terminal illness with very little hope of any treatment.

He attended counselling and after some months felt able to use his skills to help others learn about HIV. Over the following five years he visited numerous schools, workplaces and clinics to talk about HIV and use his personal experience to educate others and destigmatise HIV. He remained well until 1994 when he got TB. This was successfully treated and he was able to go back to work. His health deteriorated again in late 1995 and he had a bout of pneumonia and recurrent abscesses. He continued to be active in the PLHA network and was always very well informed about the latest development in HIV treatments, particularly ARVs. He even arranged a meeting for PLHA groups where ARVs were extensively discussed as "hope for people with HIV". Not a single person at the meeting was on ARVs or had any likelihood of ever being so. John's health has continued to deteriorate and he is unable to work. Despite having given more than seven years of his life to educating people about HIV he is now unable to buy food let alone any medication.

Stephen, a medical doctor, developed HIV related symptoms in January 1992. By March 1992 he was getting weaker, requiring frequent hospital admissions and by July he had to give up work. In February 1996 he was admitted in critical condition and remained unconscious for eight days. He was eventually discharged after three weeks reasonably well. It was then that he expressed the desire to try some of the antiretroviral drugs. He was counselled about the expense and possible side effects and decided to discuss it with the family. Initially his family discouraged him from spending such a large amount of money when he had a big family to look after. His decision was much swayed by the media stories about the protease inhibitors which were run during and after the Vancouver conference.

In August 1996 he started on indinavir and ZDV only because he could not afford triple therapy. Indinavir had to be obtained from the USA through friends, costing him about \$600 for a month's supply. He managed to acquire ZDV locally at a cost of \$200 for a month's supply. By the time he started the combination therapy he was a very sick man. No basic tests such as CD4 cell counts or viral measurements had been done. After 2 months treatment he had a bad spell where he was taking the medicines irregularly either because he was vomiting or because he was taking too many other drugs. In January he went two weeks without indinavir because his supply did not arrive in time. He was getting it through people who were travelling to Uganda to minimise on courier expenses. When the medicine did arrive he resumed taking it but now he was getting weaker. He developed septicaemia and died on February 9th 1997 with the January bottle of indinavir hardly used.

Maureen is a 28 year old single mother with two daughters, aged 3 and 5. Her husband, a police officer, died last year and his family took virtually all their possessions after the burial. "Property grabbing" is common. Maureen is a teacher and until recently was teaching the final year of primary school. With her take-home pay she was just about able to pay for the rent of her 2 room compound home and feed herself, the children and her younger sister who had come to live with her to look after the children whilst she was at work. Her house is not electrified and water is collected from a communal pump more than 100 yards from the house. She had an HIV test following her husband's death as she suspected that he had died from AIDS. He had widespread KS and eventually died of meningitis. Maureen's main concern is the future of her children. Whilst she was working, life was tolerable but now that she is too weak to work she cannot support her family. Her sister has been forced to sell sex merely to get enough money to feed them all. Maureen is aware of the "wonder drugs" that are available for people with HIV. She has read about them in the newspaper. Her concern is how can she feed her children and she is anxious about who will look after them when she dies.

Anthony, a relatively successful banker came to the company clinic after a loan to build a house for his wife and new son had been refused on medical grounds. After much heartache, he decided to be tested for HIV and found that he was seropositive. His wife was also tested and was seronegative. He wanted the doctor to get hold of antiretrovirals whatever the cost. As he earned approximately \$1000 a month he could put his entire salary into ARVs or build a house for his wife and new son. He decided to build the house and start ARVs only when he became immunocompromised. He remained well for 3 years and built his house.

By late 1995 his CD4 count had fallen to 160 and he started on ZDV and ddI. His CD4 remained stable until March 1997 when he had a severe attack of herpes zoster. He was prescribed high dose acyclovir and he made a quick and complete recovery. But by June 1997 his CD4 had fallen further. He badgered his doctor to change his regimen to include a protease inhibitor. Through an American mail order company the doctor managed to obtain indinavir at 50% the local cost. He started on triple therapy and by October his CD4 count had risen to 380 and he was remarkably well.

His "success" must in part be due to his wife. She kept him to his regimen religiously. She dealt with her own stresses in resigning herself to only one child in the face of extreme pressure from relatives (who do not know her husband is HIV-positive) to have more children. How long his good health will continue is anyone's guess.

Foreword

1996 and 1997 were marked by fresh optimism about finding a solution to the devastating problem that HIV/AIDS has come to represent - in terms of serious social and economic disruption and appalling human suffering. This new hope came from the development of a growing number of new approaches that promise a longer life, of higher quality, supported medically and socially, for people living with HIV infection. The development of new antiretrovirals (ARVs), particularly the combination therapies of three ARVs including one protease inhibitor, has been greeted with enormous enthusiasm.

WHO, in collaboration with UNAIDS, responded to these important developments with an Informal Consultation on the Implications of Antiretroviral Treatments, held in April 1997 in Geneva. As an immediate follow up to the Consultation, a set of guidance modules has been prepared for decision makers at health planning units of government ministries, major hospitals, and academic and training institutions, on major issues relating to antiretroviral treatments.

The majority of people living with HIV/AIDS in developing countries have no access to these costly treatments - they will perhaps obtain a couple of courses of antibiotics to treat opportunistic infections when these arise and if they are lucky, pain killers in the last stages of disease. Many people living with HIV/AIDS learn about the new treatments through the media, are filled with hope and prepared to mobilise whatever financial resources are needed to obtain the drugs as soon as possible. Medical requirements to ensure that the treatment can be prescribed safely and effectively may be scarcely considered. How to pay for the drugs on a long term basis and the impact on the family of devoting all resources to buying drugs are likewise secondary considerations, perhaps to be dealt with "tomorrow".

UNAIDS and WHO are committed to increasing access to new technologies which have been shown to be effective in preventing and treating HIV/AIDS and improving length and quality of life, to all those in need. We share the general enthusiasm about the remarkable advances in ARV treatments. But this enthusiasm is tempered by two major concerns: one, is their long term benefit - and only clinical experience over several years at least will provide evidence that a reliable, long term treatment has been found. The other is the accessibility of these expensive and difficult treatments to the vast majority of the world's HIV infected people, namely those living in the developing countries where resources for health care are often very limited.

New compounds are being synthesised and developed at a tremendous rate. It is our hope that cheaper and easier treatments will become available in the near future. Meanwhile, UNAIDS and WHO will regularly assess progress and disseminate information on the state-of-the-art of the new treatments, and promote and facilitate access to the drugs to all in need, through advocacy with national governments and the pharmaceutical industry, and through their international networks of researchers, health professionals, and NGOs. The guidance provided in these modules will be regularly updated to keep up with the latest advances.

Brief history

Since the human immunodeficiency virus (HIV) was first identified as the cause of AIDS, enormous research efforts have concentrated on identifying and developing compounds to suppress its replication.

In 1987, zidovudine (ZDV, formerly known as AZT) was approved by the US Food and Drug Administration. In the years that followed, four other drugs of the same family were introduced. The principal problems with these drugs, including ZDV, is their limited potency, their toxicity and their time-limited benefit - largely due to the development of resistance.

Large multicentre clinical trials then showed that double therapy with two of these drugs was superior to monotherapy in terms of disease progression and survival. Greater and more sustained decreases in plasma levels of HIV-1 RNA were achieved with double combinations.

Significantly larger reductions in viral load were achieved by adding a new class of agents, the protease inhibitors, which became available in early 1996. Over the past two years, the number of antiretroviral agents available has expanded substantially and trials of the new antiretroviral treatments, particularly the triple therapies using combinations of drugs from different classes have shown impressive short term results decreasing both morbidity and mortality and offering real hope for people living with HIV/AIDS of a longer and a better life. Consequently, combination therapy has rapidly become the gold standard of care in antiretroviral therapy.

With regimens of three drugs, over three quarters of HIV-infected patients had levels of virus in plasma suppressed to below the level at which it could be detected and this persisted throughout follow up for as long as one year in ARV naive patients with good adherence.

It is now recognised that the sustainability of the therapeutic response to ARVs depends on the level of suppression of viral replication. Regimens which only partially suppress replication will ultimately promote the emergence of resistance. The aim of therapy therefore is the full suppression of replication to below detectable levels by the most sensitive assays available. In practical terms, this implies today the use of triple therapy usually including a powerful protease inhibitor.

The latest research shows that even with sustained suppression of HIV replication, there are still reservoirs of HIV in patients under treatment. Furthermore, the virus recovered may not be latent but still replicating at a slow rate. Viable virus has been retrieved from patients who have been well suppressed on tritherapy for up to two years. Patients who are well controlled with undetectable viral loads show massive rebound viremia when for some reason (such as an accident) they suddenly stop taking ARVs.

Recent studies are reporting high levels of resistance in relatively short periods of time, even with good adherence to the regimen. Resistance develops more readily in patients who have already received ARVs and in those with low CD4 counts. The most favourable results have been obtained from studies in patients with optimal adherence. It is likely that treatment failure in normal clinical practice will be higher.

In recognition of these limitations, researchers are already seeking alternatives to triple therapy - quadruple therapy and new classes of drugs. Approaches to HIV treatment are in rapid evolution as work continues on disease pathogenesis and viral dynamics.

Critical issues in ARV treatments for HIV infection still require clarification: when to start and change treatment, and with which combinations, what drug sequence strategy to adopt. With the rapid progress in drug development, treatment guidelines are likely to have to be frequently updated. *(For current recommendations on the use of antiretroviral treatments see Module 4)*

The use of zidovudine to *prevent* mother to child transmission of HIV was shown as long ago as 1994 to be effective (reducing transmission by 50-70%). Monotherapy for the *treatment* of HIV infection is now regarded as obsolete because of serious problems of resistance.

ARVs are also used in post-exposure prophylaxis for health care workers (See Module 7). Guidelines have been developed in industrialised countries all of which recommend ARV therapy following accidental exposure to blood which may be contaminated by HIV. It should be noted that data on efficacy is limited and that the average risk of seroconversion following exposure, even without treatment, is very low. Minimising risks of exposure through strict observance of universal precautions remains the priority.

Treatment for the few: but a concern for all

The major challenges in antiretroviral treatments are access, correct and supervised use, adherence and the development of resistance. The new treatments are not available to the vast majority of the world's HIV infected people, most of whom live in the developing countries. Triple therapy is very expensive and the related services required to ensure their safe and effective use are complex. Adherence requires a strict individual protocol and reliable psychosocial and material support.

Despite this, ARVs are present in most poor countries of the world, but accessible to a very small, and in the main, wealthy, minority. Efforts to obtain the drugs, often in an irregular and haphazard fashion, may absorb the entire resources of the family. In these situations, problems of incorrect and unsafe use, unreliable supply, and a black market in both good quality and counterfeit drugs are likely to appear. This has serious public health implications because of the almost certain development and spread of resistant strains. It is therefore urgent for policy makers, ministries of health, health professionals and NGOs to address all aspects of ARV treatments including access, irrespective of the wealth and circumstances of their country.

Over and above the public health concern, UNAIDS, WHO and its member states are committed to the principle of universal access to effective treatments for all in need. All efforts therefore will be made to assess the currently available treatments, the desirability and feasibility of introducing them into national health systems in different settings, and likely future research developments; to increase access to these treatments, to press for further research into cheaper and easier regimes, to negotiate with industry to devise mechanisms to reduce prices; and to maintain and reinforce prevention and care activities for all those affected by HIV/AIDS.

WHO Informal Consultation on the Implications of Antiretroviral Treatments

In response to requests from people living with HIV/AIDS, health professionals and governments, WHO held an informal consultation on the implications of antiretroviral treatments in April 1997, in collaboration with UNAIDS. Participants included clinicians, researchers, PLHA, national AIDS programme managers, representatives of ministries of health, the pharmaceutical industry, NGOs, donors, UNAIDS, other UN agencies, and various WHO programmes. A report of the consultation* was produced in September 1997 and French and Spanish versions will be available in early 1998. The report summarised the essential points raised during the consultation and derived from discussions, presentations and background papers. The essential points raised during the consultation are summarised below; the full report is available from Distribution and Sales, WHO, 20 Avenue Appia, 1211 Geneva 27 (fax: 41 22 791 4857; email: publications@who.ch) or from UNAIDS Information Centre, 20 Avenue Appia, 1211 Geneva 27 (fax: 41 22 791 4187; email unaids@unaids.org).

Technical guidance modules

Audience

The modules are addressed mainly to “middle level” decision makers at academic and training institutions, major hospitals and district hospitals. However, in all modules there are issues which may be of concern to technical decision makers in government ministries such as health, planning or finance.

Topics

Key content areas for the modules were identified from the issues raised and discussed at the consultation. The nine guidance modules which make up the complete set are:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into health systems: economic considerations
3. Antiretroviral treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to the human immunodeficiency virus
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

The modules form a complete set which together address the major issues relating to the use and provision of ARVs but each is designed to “stand alone”. Depending on further developments in the treatments and experience with their use in different settings, there may be requests for guidance in other areas. Other modules may then be added to the set.

Summary of the Report of the WHO Informal Consultation on the Implications of Antiretroviral Treatments

Aims:

- To review the findings on ARVs - their efficacy, side effects, problems of resistance , adherence and cost benefits;
- To discuss minimum requirements for their safe and effective use;
- To examine the clinical, social, financial and ethical implications of providing ARVs, especially in low and middle income countries;
- To make preliminary recommendations.

Currently available antiretroviral drugs

Current antiretroviral agents for HIV/AIDS can be divided into **two major classes of drugs**: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs are further divided into nucleoside (NRTI) and non-nucleoside (NNRTI) subclasses. A third class, integrase inhibitors, is under development, as are drugs with other mechanisms of action (e.g. hydroxyurea, chemokines and interleukin 2).

Eleven antiretroviral agents are currently available in different parts of the world. Registration of drugs differs from country to country. Ten of these agents have been shown to be useful in the treatment of HIV/AIDS by slowing the progression of the disease and prolonging survival. Table 1 lists the currently available agents, by brand name, class and estimated market cost, based on US pricing in June 1997.

Table 1

Generic Name	Brand name*	Class	Unit dose	Cost: Three months/US\$**
didanosine (DDI)	Videx	NRTI	100 mg	420 - 700
lamivudine (3TC)	Epivir	NRTI	150 mg	690
stavudine (D4T)	Zerit	NRTI	40 mg	700 - 730
zalcitabine (DDC)	Hivid	NRTI	0.75 mg	630
zidovudine (ZDV)	Retrovir	NRTI	100 mg	720 - 860
indinavir	Crixivan	PI	800 mg	1350
nelfinavir	Viracept	PI	250 mg	1670
ritonavir	Norvir	PI	600 mg	2080
saquinavir	Invirase	PI	600 mg	1720
delavirdine	Rescriptor	NNRTI	100 mg	
nevirapine	Viramune	NNRTI	100 mg	740

*brand names may vary between countries

** ranges reflect dosing variations

Module 1

Introduction to antiretroviral treatments

Best treatment option available

Evidence has shown that a combination of ARVs including at least one PI, is the most effective treatment available to suppress the replication of HIV. This is reflected clinically, in decreased incidence of opportunistic infections, decreased hospitalisations and ability to return to normal functions of daily living. Serologically, it is reflected in decreased viral loads (often to undetectable levels) and increases in the number of CD4 cells.

Cautious optimism

As yet it is not known how long these benefits will last. Long term clinical outcomes (spanning several years of observation) have not been demonstrated; resistance may occur even with triple therapy, and “sanctuary” sites may exist where drugs cannot suppress viral replication even in individuals under treatment. In addition, when treatment is interrupted, viral rebound may occur leading to rapid clinical deterioration. Finally, in only a proportion of patients on triple therapy, with available techniques, is viral load reduced to undetectable levels.

The combination therapies are very expensive (US\$ 1000-1500 per month in May 1998) and require a rigorous and difficult daily regimen in order to avoid the emergence of drug resistance. Fifteen to twenty tablets are to be taken over the day. Unpleasant side effects are common, drug interactions have to be considered, and clinical and laboratory monitoring is required to detect adverse reactions.

Individual needs and public health considerations

During the consultation there was a shared understanding that ARVs can improve the life prospects of PLHA and that combination therapy represents the best treatment option available currently. Participants recognised the primacy of the need to respond to the individual suffering of PLHA while acknowledging concerns about long term sustainability and safety of ARVs, and responsibilities for the health needs of the general population.

Guiding principles

- Universal access to care and treatment, a principle which WHO promotes as a human right, is the ultimate aim. The fact that access might not be achieved immediately and universally does not preclude progressive introduction of ARVs, recognising that they are already present in countries. The stark contrast between industrialised countries where patients are usually receiving these treatments through public and private insurance schemes and developing countries where the majority of those requiring treatment cannot access these drugs, is ethically unacceptable.

- As an overarching ethical principle, it must be recognised that combination ARV therapy with at least 3 ARV currently represents the most advanced therapy of choice for people living with HIV/AIDS. There is therefore an obligation for governments to make every effort to increase access to these treatments within the context of national health programmes which address competing health care needs. Governments must ensure non-discrimination and equity in access among PLHA and among those living with other life-threatening conditions requiring comparably costly and complex therapies.
- The provision of ARVs must not divert resources from HIV prevention activities (e.g., control of STDs, promotion of safer sex including condoms, and ensuring a safe blood supply), the treatment of opportunistic infections, and research to develop preventive tools, particularly vaccines and microbicides. Neither should it divert resources from other essential public health programmes.
- ARV treatments must be supported by a functioning health and social system which ensures adequate diagnosis and treatment of opportunistic infections, appropriate pain management, and correct use of and adherence to ARVs to avoid the emergence of drug resistance and transmission of resistant strains.
- Adherence is a required component of effective treatment, not a precondition for access to treatment. Patients should not be excluded *a priori* from ARV treatment because they belong to groups regarded as unlikely to adhere (e.g. injecting drug users, the homeless and the poor). Health providers' roles and responsibilities in ensuring adherence must also be recognised.
- The supply, distribution and provision of ARVs require national quality assurance systems to be in place. Governments have a regulatory and supervisory role in these areas
- Cost is a major issue. Collaboration between and within countries to enable those who are most in need to obtain treatment, should be promoted and mechanisms/strategies put in place to effect such solidarity. It is ever more urgent for governments to reconsider the level of the health budget in relation to the budget for other sectors.
- Commitment to continue basic science research into drugs and clinical outcomes is essential as none of the currently available ARVs are ideal and a number of promising drugs are under development.
- The pharmaceutical industry is a key partner in health care, and has social responsibilities as do all civil organisational and institutional bodies. Their collaboration is essential.
- Prevention and care are two sides of the same coin. All prevention efforts reduce or limit the final number of infected people needing care. Whenever care is provided, there is a golden opportunity to provide or reinforce prevention education.

Minimum requirements

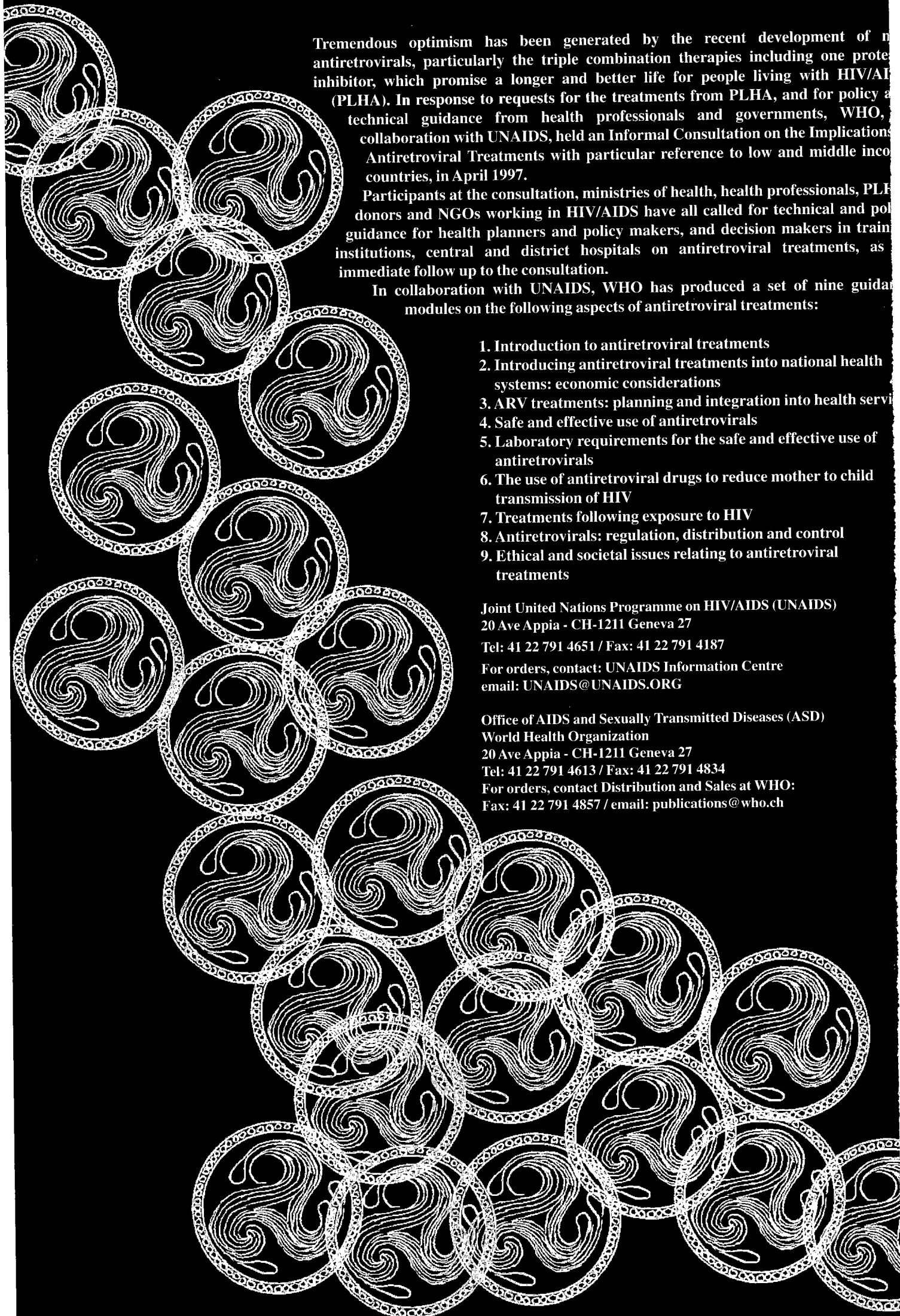
- Availability of reliable, inexpensive tests to diagnose HIV infection and access to sites providing voluntary and confidential counselling and testing.
- Adequate management of opportunistic infections including availability of affordable drugs for their treatment and prophylaxis.
- Laboratory facilities to monitor adverse reactions including liver function test, complete blood count, amylase, and electrolytes.
- Appropriate training for clinicians and nurses in the correct use of ARVs.
- Support of a social network to help patients adhere to the regimen.
- Strengthening of health and social services in a continuum of care, from the home, through community health centres, to district/city hospitals, with flexible and timely referral and co-ordination procedures; provision of material and psychosocial support for those taking ARVs at various levels of the continuum,
- Reliable, long-term and regular supply of drugs at the health centre level.
- Joint decision making between physician and patient on all aspects of ARV treatment, including the decision to begin ARVs.

Recommendations

- Long term affordability based on scenarios which assume full coverage and total adherence is not achievable at present in most countries. A useful approach might be to ensure access at a limited number of centres of excellence where clinical, laboratory and social support can be guaranteed. Allocating different therapies to subsets of people with HIV-related conditions (e.g. ARVs for prevention of MTCT and PEP), taking into account the realities of different settings, may represent a rational strategy offering affordable starting points.
- Because of the high daily turnover of virus production, resistant strains develop very easily. Strict adherence to the drug regimen is therefore essential. Emergence of resistance should be carefully monitored through a network of collaborating laboratories. WHO/UNAIDS could establish such a co-ordination mechanism.
- In order to minimise unregulated supply and distribution leading to irregular provision, unsupervised use and the emergence of resistance, there need to be effective national drug regulatory authorities.
- The diagnosis and treatment of opportunistic infections remains an essential component of the clinical management of HIV/AIDS patients. As in the recent revision of the WHO essential

drug list in December 1997, governments should also consider adding drugs for opportunistic infections, other HIV-related conditions and pain management to their Essential Drugs Lists.

- International technical agencies and programmes should collect and widely disseminate information on all aspects of ARV treatments including the drugs themselves, rational approaches to problems of adherence and resistance, prescription guidelines, health system requirements, pricing policies and financing options.
- Clinical studies in all countries should follow a basic set of ethical guidelines. All clinical trials should aim to provide meaningful estimates of the gain in quality-adjusted life years, reflecting not only changes in survival but also improvements in the quality of life.
- The currently available nucleic acid amplification assays (DNA and RNA) used to measure viral load are not equally sensitive and/or equally efficient in amplifying all known HIV subtypes. The tests need to be improved to allow accurate detection of the HIV variants most prevalent in Africa, Latin America and Asia. The standardisation of these assays is also an urgent priority.
- Viral load measurement is highly desirable to monitor efficacy of ARV treatments in asymptomatic patients.
- Operational research on how best to implement ARV treatments in settings where resources are limited and adherence beset with difficulties, is needed in low and middle income countries.
- Training of health professionals in the correct use of ARVs is essential if the decision to introduce them is made. Clinical guidelines should be developed for professional use. Training should be undertaken to reach all care providers as a team.



Tremendous optimism has been generated by the recent development of new antiretrovirals, particularly the triple combination therapies including one protease inhibitor, which promise a longer and better life for people living with HIV/AIDS (PLHA). In response to requests for the treatments from PLHA, and for policy and technical guidance from health professionals and governments, WHO, in collaboration with UNAIDS, held an Informal Consultation on the Implications of Antiretroviral Treatments with particular reference to low and middle income countries, in April 1997.

Participants at the consultation, ministries of health, health professionals, PLHA donors and NGOs working in HIV/AIDS have all called for technical and policy guidance for health planners and policy makers, and decision makers in training institutions, central and district hospitals on antiretroviral treatments, as well as immediate follow up to the consultation.

In collaboration with UNAIDS, WHO has produced a set of nine guidance modules on the following aspects of antiretroviral treatments:

1. Introduction to antiretroviral treatments
2. Introducing antiretroviral treatments into national health systems: economic considerations
3. ARV treatments: planning and integration into health services
4. Safe and effective use of antiretrovirals
5. Laboratory requirements for the safe and effective use of antiretrovirals
6. The use of antiretroviral drugs to reduce mother to child transmission of HIV
7. Treatments following exposure to HIV
8. Antiretrovirals: regulation, distribution and control
9. Ethical and societal issues relating to antiretroviral treatments

Joint United Nations Programme on HIV/AIDS (UNAIDS)
20 Ave Appia - CH-1211 Geneva 27

Tel: 41 22 791 4651 / Fax: 41 22 791 4187

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