

WHO/ASD/98.1  
UNAIDS/98.7  
Distr: General

# Guidance Modules on Antiretroviral Treatments

Module 9

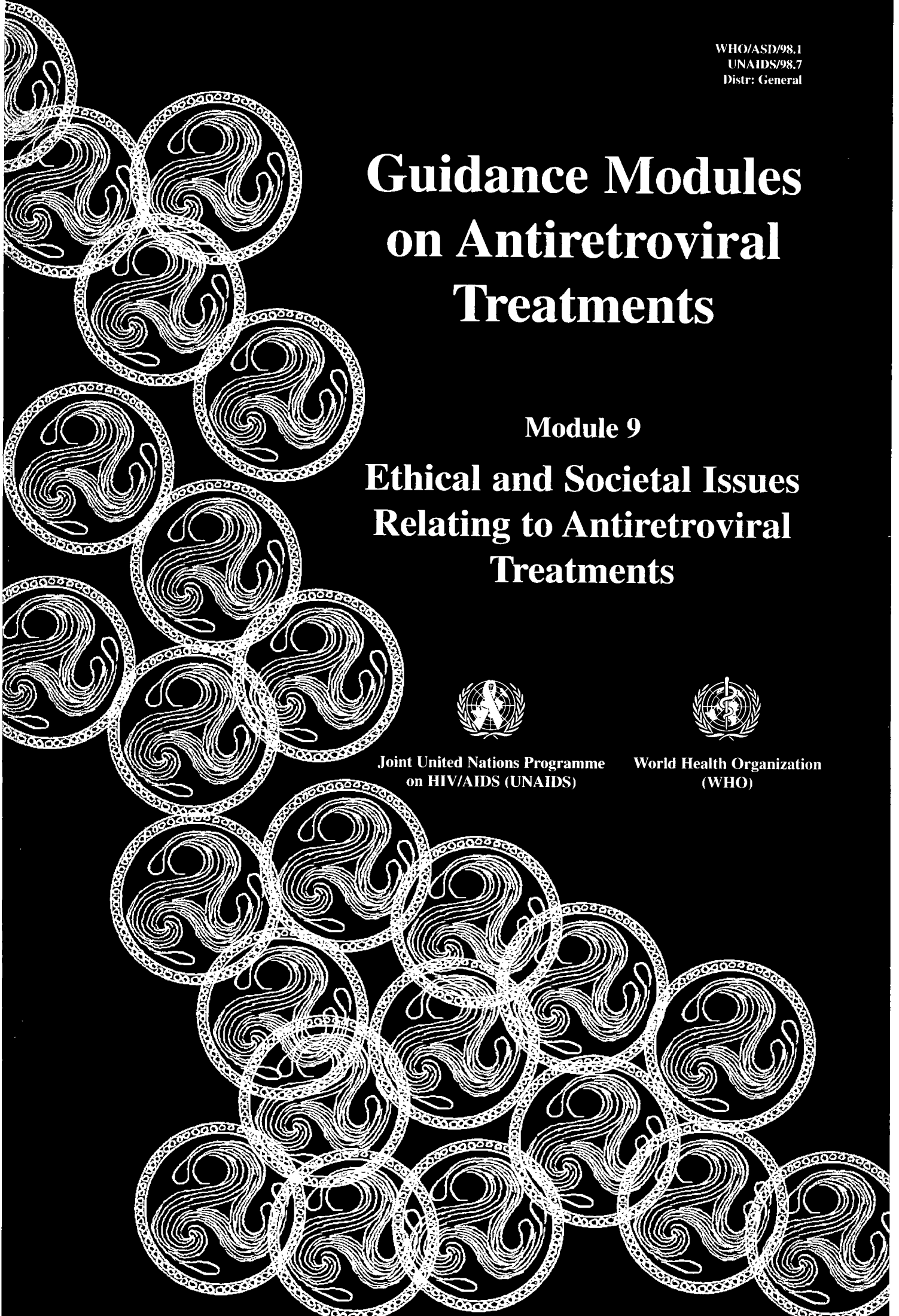
## Ethical and Societal Issues Relating to Antiretroviral Treatments



Joint United Nations Programme  
on HIV/AIDS (UNAIDS)



World Health Organization  
(WHO)



## **Acknowledgements**

The World Health Organization and UNAIDS would like to thank Dr Ronald Bayer, Columbia University School of Public Health, New York, USA for preparing the text of this module;

Dr George Browning, University of Glasgow, Scotland, UK, Dr Jonathan Mann, Harvard School of Public Health, USA, Dr Kevin De Cock, Centers for Disease Control, Atlanta, USA, Father Michael Kelly, Kara Counselling and Training Trust, Lusaka, Zambia, Mr David Chipanta, Global Network of PLHA, Lusaka, Zambia and Mr David Patterson, Policy, Strategy and Research, UNAIDS, for their most thoughtful reviews of the draft text; and

Dr Rachel Baggaley, Dr Susan Fernyak, Ms Alison Martin Katz, Ms Marguerite Nguyen, and Dr Eric van Praag, Office of HIV/AIDS and Sexually Transmitted Diseases, WHO, and Dr Joseph Perriens, Policy, Strategy and Research, UNAIDS, for coordinating the project.

## **©World Health Organization and Joint United Nations Programme on HIV/AIDS, 1998**

This document is not a formal publication of the World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS), and all rights are reserved by them. The document may, however, be freely reviewed, abstracted, reproduced, or translated in part, but not for sale or for use in conjunction with commercial purposes. It may also be reproduced in full by non-commercial entities for information or for educational purposes with prior permission from WHO and UNAIDS.

For authorization to translate or reproduce the work in full, and for any use by commercial entities, applications and enquiries should be addressed to the Office of HIV/AIDS and Sexually Transmitted Diseases, World Health Organization, 1211 Geneva 27, Switzerland, which will be glad to provide the latest information on any changes made to the text, plans for new editions, and the reprints and translations that are already available.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by either WHO or UNAIDS in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The views expressed in these documents by named authors are solely the responsibility of those authors.

## **Module 9**

### **Ethical and Societal Issues Relating to ARV Treatments**

#### **Introduction**

Advances in the treatment of HIV-related disease made during the last two years mark what may be a fundamental change in the capacity to manage what had been considered a uniformly fatal condition. Following the Ninth International AIDS Conference in Berlin, where results of the Concorde zidovudine trial were presented, many expressed despair over finding a treatment for HIV-related disease. With the introduction of combination and antiretroviral treatment, hope has been renewed. In the advanced, industrialized nations, combination therapies (usually two nucleoside analogues and a protease inhibitor) have become the standard of care.

At the Eleventh International AIDS Conference in Vancouver, July 1996, researchers presented evidence suggesting the possibility of dramatically reducing the viral load of HIV-infected individuals with combination therapy using at least three ARVs. Such an achievement, it was suggested, could extend periods of symptom-free life and life expectancy. Subsequent clinical reports confirmed the dramatic impact of the new ARV therapies. There was speculation about the prospect of eradicating infection in those already carrying HIV. Unfortunately subsequent research has shown that this is very unlikely. However, the popular media in the USA and other economically advanced nations came close to declaring victory in the struggle against AIDS and this has dramatically altered perceptions about AIDS as a uniformly fatal disease.

Some have remained skeptical, recalling the ultimately unfounded enthusiasm for monotherapy with ZDV but for many clinicians and hundreds of thousands of their patients, a new era of treatment has begun.

#### **Ethical challenges**

The new sense of therapeutic efficacy has produced ethical challenges in both advanced industrial countries, and in resource-constrained countries where the vast proportion of people with HIV infection live.

Much discussion of health policy generally, and of the challenges posed by ARV therapy more specifically, centres on questions of fact: How much will new treatments cost? How much of gross domestic products or of health care budgets would be required to meet the needs of some or all who might benefit from therapy? What kind of assistance would be needed to make the provision of ARV therapy possible in resource-constrained countries and at what level? These are important questions which can be answered empirically. But as important are questions of ethics. What do nations owe to their citizens who are critically ill in terms of provision of health care and other social support? Is health care a right? And if it is a right, how extensive are its claims? How should the needs of those with HIV infection be balanced against those with other medical

conditions? When insufficient resources are available for all to benefit from ARV therapy, would it be acceptable for some to benefit? How should such selections be made? Do the wealthy nations have an obligation to assist less developed nations in gaining access to ARV therapy? If they do, what level of assistance would satisfy such an obligation?

Each of these questions presents decision makers with difficult choices about what ought to be done given available resources. These decisions must involve ethical considerations which, in turn, reflect deeply held moral conceptions of the obligations of nations to their citizens. Because decision makers, communities, health professionals and individual patients have different values, interests and responsibilities, these ethical choices may require difficult trade-offs. Thus, for example, a commitment to maximize equality will often require some compromise with a commitment to maximize liberty.

### **Different ethical questions for rich and poor nations**

The new therapeutic advances are available and socially affordable only in the advanced industrial nations. In these nations, ethical questions will surface as governments must determine whether they will extend the benefits of ARV treatment to all who could benefit despite the high costs involved. Furthermore, it will be necessary to confront the question of whether concerns about viral resistance induced by poor adherence to complex regimens can justify a refusal to prescribe ARVs to those who request them. In short, in the industrialized nations the new ARVs will pose challenges to the principle of justice, which requires a fair distribution of health care services, and to the principle of autonomy, which requires respecting the preferences of individuals when those preferences do not impose burdens or harm on others. In poorer nations, the picture will be very different. The new therapies will be largely beyond reach, and decision makers will be required to determine how severely limited national resources can be used to fund continued HIV prevention efforts and the palliative care and social support of those suffering with advanced HIV disease. They will have to make difficult rationing decisions regarding access to ARVs in situations of extreme resource constraint.

In the end, the gulf between the therapeutic prospects in the wealthiest nations and the poorest nations will compel the global community to confront the question of what obligations exist across borders to assist those with HIV infection.

### **Antiretrovirals: the high cost of progress**

The new combination therapies are costly by any standard. In the United States, the addition of protease inhibitors to the therapeutic armamentarium has tripled retail prescription costs of drugs used in treating HIV disease, bringing the average to US\$10,000-\$15,000 per year, per patient. The viral load assays necessary to monitor the drugs' effectiveness add further expense. In the USA, which, unlike other advanced industrial nations, does not have a national health insurance programme that covers all citizens, scientific progress represented by ARV combination therapy has compelled government officials to confront the limits of the patchwork of programmes

designed to assure access to HIV-related services. Despite the rapid increase in funds for such purposes, many thousands of patients have been unable to afford treatment. The ethical challenges posed by such restrictions are fundamentally different from those that will confront policy makers and clinicians in nations where more than 90% of the world's HIV infected people live.

It has been estimated that if all those who could benefit from such treatment were to receive it in Sub-Saharan Africa, Southeast Asia, and Latin America, at current prices for drugs, the cost would be US\$ 101.9 - US\$ 161.4 billion, US\$ 57 - US\$ 90.2 billion, and US\$ 9.1 - US\$ 14.4 billion respectively. To place these figures in context, the costs were compared to both total health expenditures and gross domestic product for each region. In Sub-Saharan Africa, the costs of ARV treatment would represent 1763% of current health expenditures and 66.9 % of gross domestic product. In Southeast Asia, the costs would represent 364% of total health expenditures and 14.6% of gross domestic product. For Latin America the costs would represent 23.9% of total health expenditure and 1% of gross domestic product.

These extraordinary and obviously unaffordable sums understate the case. They do not include the cost of critically important provision of treatment for opportunistic infections, palliative care for those who do not respond to the new treatments, and the costs of social and psychological support to those dealing with a burdensome disease, and a complex medical regimen.

Only a radical reduction in the price of drug therapy and massive assistance from the wealthiest nations of the world could begin to alter this grim picture.

### **Drug pricing**

How should one consider the fairness of prices for therapeutic agents, and especially for drugs that may critically affect the life prospects of individuals afflicted with a fatal disease? Advocates of a market approach assert that regulation of prices is not only unnecessary but would be counterproductive. "The basic principle governing the free enterprise system is that free and unrestrained competition should force fair prices. The more segmented the industry, the truer that is, and the pharmaceutical industry...is highly competitive." Those who reject the market as the sole arbiter of drug prices note that for many drugs the patents granted as a way of encouraging research and investment create a monopoly situation within which the market cannot function effectively. In the face of a lethal disease, the only limit on what will be paid for a drug is the limit that prices impose on desperation-driven demand. The resultant price may, nevertheless, be very high indeed. In a careful reflection on the competing claims involved, Baruch Brody has concluded, "We need to develop a system of drug pricing that provides adequate economic incentives for drug research and development...while limiting excessive promotional costs and profits."

Appeals to a sense of moral responsibility may have some impact on pricing policy by pharmaceutical firms, but inevitably it will take intervention on the part of governments to create a regulatory context that will limit the tendency to "excessive promotional costs and profits."

What is crucial at this juncture is to recognize that the market price is not necessarily the fair price. Once that is recognized, it will be possible to engage in open and vigorous debate about how best to determine the fair price of drugs, crucial to the lives of sick people. One approach to the current untenable situation that places ARVs beyond the reach of those who might benefit from them would be for international organizations to undertake bulk buying agreements that would create a market context conducive to a significant lowering of prices.

### **International assistance**

Even a radical reduction in the price of drugs will not resolve the problems confronted by the poorest of nations. Only significantly increased international assistance could begin to remedy this situation, however partially. While a right to health is enshrined in international covenants, vast inequities in the patterns of morbidity and mortality exist globally. Men, women, and children in the poorest nations routinely die of diseases that are treatable such as diarrhoea, acute respiratory infections and often still, TB.

Whether conceptualized as a moral duty or as an obligation to provide charitable assistance, the wealthy nations of the world can do far more to meet the burden of disease in the poorest nations. That they have failed to do so stands as a striking failure to respond to the desperate needs of the vulnerable. Typically, analysis of this problem from an ethical perspective focuses on the assurance of subsistence assistance that can guarantee the basic conditions for health and well being. Having failed to address these conditions, it is hard to imagine the kind of assistance that would be required to make access to very costly ARV therapies possible. A final dilemma that must be noted confronts donors who wish to provide ARV-related assistance. According to some conceptions of ethics, those who are the least advantaged have claims to priority when aid or assistance is considered. Yet in this instance it may be that assistance to nations that are more advantaged will make possible the provision of ARV treatment to a restricted number of citizens while the most impoverished nations would require much greater levels of assistance than are available to make any effective use of ARV treatment.

### **Access to antiretroviral treatment in resource-constrained nations**

Given the cost of ARVs and the remote prospect that either international assistance or adjustments in drug pricing will fundamentally change the parameters that now prevail, many nations will need to approach the question of treatment for HIV infection with extremely limited capacity. In each nation, decisions about provision of ARVs will have to be made within broad sectoral determinations, e.g., the proportion of public resources that will be available for health care, education, social welfare, domestic security, national defense and other sectors. Even within the health sector, decisions will have to be made among competing claims, e.g., AIDS, malaria, maternal and child health. And within budgetary resources available for AIDS, choices will need to be made regarding allocations for prevention, the treatment of opportunistic infections, palliative care and ARVs. In the poorest settings, ARVs will be all but unavailable. A recent report from Uganda thus declared, "Antiretroviral drugs are not available in government health

institutions nor in those run by religious organizations. Their availability is limited to private pharmacies or through direct ordering through various suppliers outside Uganda." On the other hand, in nations such as Brazil and Thailand, resources are sufficient to make possible government funded programmes guaranteeing access to at least some ARV treatments for certain groups. It is within these nations where resources permit some commitment of public funds to ARV treatment that it will be necessary to address the following questions:

- How does antiretroviral therapy link to broader health sector and community development objectives?
- Which, of the available alternatives, are realistically affordable given the country's resource constraints?
- Which of the affordable alternatives are most efficient in achieving a favourable development impact?

Empirical analysis will provide answers up to a point. But in the end these are fundamental policy and ethical choices. It will be crucial to recognize that there may be no right answers, and from an ethical perspective there may be some answers that are troubling and even violative of basic conceptions of fairness.

### **Levels of basic care**

At its most fundamental level, the principle of justice requires that within a given society no individual be deprived of access to effective, socially affordable, medical treatment because of his or her inability to pay for such services, and that whatever patient costs are associated with care not represent an undue burden. Nations will differ as to how much they devote to health care as compared to other social needs. They will differ in terms of how much they devote to curative, as compared to preventive, interventions. Different countries will have different notions of the basic care to which each individual is entitled. Given available resources, no single standard can be applied to all countries. Nevertheless, some levels of general health provision may be so low, given the resources generally available, as to represent a violation of the obligation to assure a level of basic care to all.

### **The greatest good to the greatest number**

In general, those interventions that will save the most lives or reduce suffering to the greatest extent have a stronger ethical claim than those that will benefit fewer individuals. There is, however, no easy way to measure and compare degrees of suffering. Nor are there simple ways to compare reduced suffering with extended longevity. Those responsible for allocating very scarce medical resources are thus engaged in a calculus of misery that requires an open, careful, and public weighing of the choices they must make. No single ethical principle exists that could resolve the current dilemmas.

Given these general considerations, it is clear that no policy that subjects AIDS care to invidious discrimination can be justified in ethical terms. Thus, for example, in societies wealthy enough to support dialysis for end-stage kidney disease, it would be ethically unjustifiable to deny access to ARVs, the cost of which is lower.

### **All or none?**

Once a society has established an adequate, basic level of health care for its members, there remains the question of whether those with resources should be permitted to purchase that which is not otherwise provided. There are some conceptions of justice that claim that health care that is not available to all should not be available to any. According to this conception of justice, a multi-tiered health care system is, by its very definition, unjust. Others have asserted that such egalitarian requirements are incompatible with the willingness to tolerate differentials in wealth and income.

### **Let those who can pay, obtain treatment?**

The issues posed by these competing conceptions of justice have special relevance to the dilemma posed by ARVs in poor nations where such therapy is not generally affordable. Should those who can afford such therapy for HIV disease be permitted to purchase the needed drugs for their own use? Should physicians trained, at least in part at the public's expense, be permitted to dispense such drugs? Should governments supervise the provision of care to assure that it meets currently accepted international and scientific standards? Those who claim that individuals should be permitted to gain access to treatments not otherwise available warn of black markets in the face of restrictions. They argue that it would be cruel to deny individuals the right to use their own resources to extend their lives and the lives of family members. There are remarkably few voices arguing the case for an egalitarianism that would require all to share a common trajectory of HIV fatality.

### **Rationing under circumstances of scarcity**

When, because of severe economic constraints, it is impossible to provide ARVs in the combinations now considered the standard of care in economically advanced nations to all individuals who might clinically benefit, it might, nevertheless, be both cost beneficial and ethically defensible to provide access to selected classes at public expense. This is the classic circumstance of rationing: when all cannot be served, is it justifiable to aid the few? If such aid is justified, on what morally defensible ground does the selection process occur?

### **Special cases**

A case can be made for the identification of numerically restricted classes of individuals who could benefit from the time-limited prophylactic use of ARVs. Three groups will be discussed in

this regard: health care workers exposed to the infected blood of their patients, the victims of rape, and pregnant women.

### **Health workers**

Should health workers, who have been exposed to the infected blood of their patients, be offered ARV treatment to reduce the likelihood that they will become infected? Would the provision of such treatment to health care workers, when their patients do not have access to ARVs, be unfair?

The risk of transmission of HIV-infection by accidental needle stick wounds is approximately 0.3%. A recent study has suggested that the immediate initiation of treatment with ARVs may reduce that risk by upwards of 75%. Such treatment is normally prescribed for one month. The case for the provision of such prophylactic intervention takes the following form: first, health care workers are needed to care for hospitalized patients with HIV disease. If, in the course of their work, they are exposed to HIV and, as a consequence, become infected, develop disease, and are lost to the pool of workers capable of caring for patients with HIV infection, then society in general, and patients with HIV in particular, would lose out. Thus, patients who themselves do not have access to ARVs have an interest in prophylactic provision to health care workers. Second, if the failure to provide post-exposure prophylaxis would reduce the willingness of health care workers to care for patients with HIV, then both society and patients with HIV would have an interest in permitting this limited intervention. Third, society has a special responsibility to those who assume even limited risks associated with caring for those with HIV infection. A final claim on behalf of post-exposure prophylaxis is that since the number of eligible individuals would be relatively small, the cost incurred by such an effort could be affordable in at least some resource-constrained countries. This position has been challenged by some economists who have asserted that post-exposure prophylaxis is not cost-effective in any setting, even the wealthiest. In the end, a decision must be made about whether the unique moral claims posed by exposed health care workers warrant an intervention that cannot be justified on narrowly economic grounds.

There is a further ethical complication in the special claims of exposed health workers. The arguments could logically be extended to assert that when prophylaxis fails, treatment with ARVs should be continued. Once ARV therapy with a potential for life-extending benefits is begun, can it rightfully be interrupted? Would not such an interruption represent a kind of cruelty? Hence a case would have been made for a special class of individuals in terms of ongoing treatment. The strength of the argument for access to ARVs in post-exposure circumstances lies in limiting the intervention to the purposes of prophylaxis. Failure to do so would create a privileged class with access to treatment based on how they became infected, and that would raise profound questions of fairness.

### **Victims of rape**

Based on studies involving health care workers accidentally exposed to HIV infected blood from their patients, it is assumed that victims of rape may also benefit from ARV prophylaxis designed

to reduce the risk of HIV infection. Victims of rape have a special claim based on the profound assault to which they have been subjected. To the extent that a society can afford to provide treatment that could, at a minimum, reduce the risk of infection with HIV, it ought to respond to that unique circumstance. But, unlike the case of exposed health care workers, where it is almost always possible to determine the source-patient's HIV status - and thus weigh the cost/benefit of initiating intervention - it may not be possible to determine the HIV status of the rapist, who may not be apprehended in time or may never be identified. This would be possible with PCR and serology on semen but these tests are very unlikely to be available for cases of rape in developing countries. Therefore, the offer of post-rape prophylaxis would unfortunately concern a large number of women and would entail a significant cost in very resource-constrained societies. In societies where resources are not so limited, the moral claims of rape victims are strong indeed.

The discussion of those who have been raped quite naturally leads to the question of whether ARV prophylaxis ought to be available to those who believe they may have been exposed to HIV in consensual sex, either because of condom breakage or because of a failure to employ condoms during sexual intercourse. Those who claim that no distinction ought to be made between such individuals and rape victims wish to avoid the implication that the former are "guilty" while the latter are innocent. Proponents of treating rape victims present two arguments: First, the special claim of rape victims stems from the trauma to which they have been subjected. It may be argued that those placed at risk by consensual sex must assume responsibility for such risk (such as condom breakage) which any consenting adult assumes today in his or her sexual relations. Secondly, there is a fear that treating ARV prophylaxis as a "morning after" intervention may subvert prevention messages that stress the importance of practicing safer sex and the avoidance of unprotected sexual intercourse with those whose HIV status is unknown.

### **Pregnant women**

In 1994, a clinical trial (ACTG 076) in the United States and France demonstrated that the provision of ZDV monotherapy during pregnancy (oral therapy during pregnancy, intravenous ZDV during labour and oral therapy for the newborn for six weeks after birth) could reduce by 66 percent the risk of vertical transmission of HIV. This finding represented the first indication that ZDV could serve so critical a preventive function. Soon after those results were made public, treatment with ZDV became the standard of care for infected pregnant women in the United States. In 1988 it was demonstrated that a one month course of oral ZDV during the last month of pregnancy could also reduce the risk by around 50%. The importance of combination therapy with ARVs (including a protease inhibitor) for all infected women, whether or not they are pregnant, for the treatment of HIV infection, was convincingly demonstrated in 1995.

In settings where ARV therapy is not available for all infected women, the question arises whether it would be ethical to offer ZDV to pregnant women for the sole purpose of reducing the risk of vertical transmission? Some nations, too poor to afford ARV treatment for all who could benefit, might be able to afford the much more limited expenditure of resources that would be entailed in the preventive use of ZDV during pregnancy - although there is controversy on this matter.

Some believe that offering treatment to women only during pregnancy and solely for the purpose of reducing the risk of vertical transmission would represent an immoral transformation of women into mere "vessels of reproduction." Further, they argue that to stop treatment once it had started would be cruel. Advocates of the special treatment of pregnant women argue, on the other hand, that such efforts offer a woman the unique opportunity to save the life of her child; that the interruption of treatment after delivery would simply return her to the status of her compatriots who share the burden of living in conditions that do not permit ARV treatment. Finally, advocates stress that the offer of special treatment during pregnancy entails no obligation to accept treatment in the interest of the child. They note that while some women might refuse to accept such treatment, many would not. Thus, they assert, respect for women is best demonstrated by offering such intervention where affordable rather than withholding it because of concerns about the interests of women as a vulnerable class.

By way of summary, where resources do not permit universal treatment with ARVs, it is ethically permissible to provide such care to some special sub-groups whose claim to intervention may set them apart from the general population. The cases described above entail interventions of limited duration, designed to serve the function of prophylaxis. No strong ethical arguments can be made to give special priority for *treatment* to groups for whom *prophylactic intervention* might provide a clear benefit. Under such circumstances, open and candid discussion of why decisions have been made will provide the surest guarantee against arbitrariness and invidious discrimination.

### **ZDV monotherapy for treatment of HIV infection**

In economically advanced nations, antiretroviral monotherapy is now regarded as substandard because of the pattern of HIV resistance that develops thus limiting the effectiveness of therapy for the patient and raising the spectre of resistance to antiretroviral therapy on a population-wide scale. Can therapy, which is suboptimal in economically advanced nations, be acceptable in resource-constrained nations? The answer to this question requires a careful clinical assessment of the benefit for the individual of monotherapy and of the epidemiological risks entailed. To the extent that monotherapy offers the prospect of some, albeit limited, benefit to a patient, such therapy should be offered after a full, culturally appropriate explanation of the risks and benefits of such treatment. It would be difficult to justify, either clinically or ethically, depriving patients of the limited benefits of monotherapy because of the far greater benefits of multi-drug ARV therapy, which is utterly inaccessible. The risks of community resistance are present under such circumstances and should be weighed against the benefits to patients of monotherapy and the limited prospect that other therapies will become available which will be ineffective because of resistance.

### **Paternalism, public health, and the problem of resistance**

Where resource constraints do not provide a barrier to care, it may be necessary to consider the question of whether some patients should be denied ARVs for clinical and public health reasons.

For decades, the problem of securing adherence to extended treatment regimens for chronic conditions has been the subject of clinical concern as studies have consistently demonstrated low rates of adherence. Given such difficulties, the challenges involved in combination ARV therapy for HIV disease are daunting. Full regimens may require up to 15-20 pills daily. Some of these drugs must be taken on an empty stomach, others following a meal. Side effects, which may include nausea, diarrhoea, vomiting and anorexia, may make adherence even more difficult.

### **Non-adherence and the development of resistance**

Inadequate adherence has profound implications. A rapid rate of viral replication, combined with a high rate of mutation, can lead to the development of resistance particularly in the presence of selective pressure by antiretroviral therapies. Resistance can develop if drug doses are inadequate or doses are missed. In early trials of protease inhibitors, patients received sub-optimal dosages, and HIV readily developed resistance which persisted even when higher doses were administered. Another unfortunate result can be cross resistance to alternative HIV treatments not yet tried.

### **The individual's right to treatment and the public health interest**

The prospect of resistance not only makes individual patients vulnerable to strains of HIV that are unresponsive to treatment but raises the spectre of a public health threat that could neutralize recent therapeutic advances.

The threat of the emergence of drug resistance as a result of non-adherence raises profound ethical questions. Should some therapies not be offered to patients who might have difficulty in adhering to the demanding regimens? Should such concerns ever be cause for denying drug therapies to patients who request them? Should decisions to withhold combination therapies be based on demonstrated non-adherence with previous treatment demands or on predictions about future behaviour based on defined patient characteristics? Are there entire classes of individuals, eg., the homeless, those suffering from certain types of mental illness, or injecting drug users, to whom the drugs ought not be offered?

### **Overriding patients' wishes for their own good?**

Can predictions about patient adherence ever provide a justification for denying individuals treatment because of concerns about how the prospect of resistance would affect their own well being? From some ethical perspectives, the principle of autonomy must always guide clinical decision making. A patient fully informed of the risks of non-adherence must, from this perspective, be given the opportunity to take those risks in light of the potential benefits of therapy. Alternatively, those who believe that physicians have an ethical obligation to protect their patients' well being, even when that entails overriding patient preferences, assert that denial of access to ARVs can be justified on grounds of paternalism. Those who adhere to the paternalistic position argue that it would represent an abrogation of professional responsibility to prescribe ARVs under such circumstances.

## **Protecting third parties**

The issue is clearly not one of individual patient welfare alone. Failure to adhere to therapy may have profound public health consequences, most notably the development of resistant strains of HIV which could be transmitted to sexual and needle sharing partners as well as to the infants born to infected women. From this perspective, the issue is not a matter of limiting autonomy in order to protect the patient from the consequences of non-adherence, but is rather the protection of third parties from potential harm.

## **ARVs present a unique conflict**

Even those who are committed to the protection of patient autonomy recognize that autonomy is not an absolute and may be overridden when the wellbeing of the community is at stake. Typically, this occurs in the context of infectious diseases, such as tuberculosis, where patients may be compelled to undergo testing and treatment. The interests of the public health and the patient are served by such mandatory measures. What makes the ARV situation so unique and so potentially troubling is that the public health interest may, in some circumscribed circumstances, be placed in conflict with the preference of the patient *for* therapy.

## **Poverty and homelessness as factors in non-adherence**

Denial of access to therapy, whether on public health or paternalistic grounds, should never be based upon broad social characteristics such as mental illness, homelessness or drug use, but should only follow a careful individualized assessment of the likelihood of non-adherence. It is especially crucial to guard against the influence of preconceptions that may bias clinical decision makers against entire classes of patients. When patients are denied access to treatment, they must be apprised of the rationale for withholding therapy, and such decisions must be reviewed periodically, as changed patient behaviour could affect further clinical decisions. To the extent that social circumstances such as homelessness or inadequate access to mental health services or drug abuse treatment, create the context which threatens adherence, justice demands that those underlying conditions be addressed. It would be a cruel irony to deny the most vulnerable and marginalized access to potentially life-extending therapies when remediable social conditions contribute to their inability to adhere to therapies.

## **Directly Observed Therapy: a useful approach with ARVs?**

The problem of resistance induced by non-adherence has been at the centre of discussions regarding tuberculosis for more than four decades. With the increase in tuberculosis in the late 1980s--driven in part by the HIV epidemic--and the prevalence of multi-drug resistant tuberculosis, directly observed therapy (DOT) emerged as the standard of care internationally. Under DOT, patients are required to take their medication in the presence of a health care worker or person charged with the responsibility of assuring that individuals in fact take their prescribed medication. Viewed as an intrusion by some, as a service by others, DOT was thought to be the only way to ensure that patients continued to take their medication for the many months during

which they no longer felt sick but were not yet cured. The sheer logistics of combination therapies involving ARVs, which require, at this juncture, medications several times a day over very extended periods, perhaps life-long, preclude DOT as a useful approach. Programme planners must, however, draw lessons from the experience of DOT in the creation of clinical and social support networks that enhance the prospects of treatment adherence.

### **Physicians' responsibilities in maximizing adherence**

Finally, the threat of viral resistance must also be understood in the context of physician practices. Failure to provide appropriate combinations of ARVs at appropriate dosage levels could produce resistance even in patients who are completely adherent. Thus, there is a strong professional obligation among physicians to understand how these drugs should be prescribed. Physicians must be supported in their efforts by institutional mechanisms that provide appropriate, ongoing education and the necessary tests that will permit the careful monitoring of patients undergoing ARV treatment. For example, careful monitoring of the clinical course of women being provided with ZDV monotherapy for the prevention of vertical transmission would limit the extent to which such medication might be diverted to other patients for the inappropriate treatment of HIV infection with ZDV monotherapy.

To the extent that resources permit, public health authorities should monitor the prevalence and patterns of drug resistant HIV so that the impact of physician practices and patient behaviours may be tracked. Furthermore, in the face of severely constrained resources, knowledge about patterns of resistance could shape the most appropriate use of health care funds.

## **Ethics in antiretroviral research**

### **Benefits for the subjects used in clinical trials**

Since so much of the contemporary approach to HIV infection is based on therapeutic agents and regimens that place treatment beyond the reach of all but the wealthiest of nations, one approach to remedying the situation is to undertake research to develop less costly therapies. From this perspective, it becomes clear that the longstanding ethical principle that research in poor countries must ordinarily involve therapies that will be affordable, if proved effective, must remain fundamental. No level of risk in research that will produce findings that cannot benefit the subject population is ethical.

### **Stopping treatment at the end of the trial and the danger of viral rebound**

While there is broad consensus on such general principles, controversy arises in particular cases where competing ethical norms provide no easy guide to decision makers. How, for example, is one to consider the ethics of research that provides to one group of subjects the current standard of double or triple combination ARV therapy when it is clear that at the end of the study such

therapy will be withdrawn from the study population? On a clinical level, it is understood that the termination of therapy will almost certainly result in an abrupt rise in viral load and a rebound in disease. Does this violate the principle established by the Council for International Organizations of Medical Services that research should never leave subjects worse off than before the study trial commenced? Does a fully informed, culturally appropriate consent, which explains the risk entailed, make it ethically acceptable? Does the additional risk, beyond that which would have prevailed in the absence of the clinical trial, fall within acceptable bounds given the potential benefits of the research? Is there an obligation for sponsoring agencies to provide those who received the multi-drug ARV arm of a clinical trial with continued treatment even when such care is not generally available to the population from which the research subjects were drawn? Clearly these issues require the attention of ethical review panels in both sponsoring and host nations.

### **Placebo-controlled trials of ZDV in pregnant women in poor nations**

It is widely acknowledged that the regimen used in clinical trial 076 is unaffordable for most women with HIV infection. Therefore, trials of modified approaches to preventing the vertical transmission of HIV have been conducted. Research on vertical transmission of HIV took place under morally troubling conditions: the gross inequalities in global access to ARVs. The dispute centred on the question of whether a placebo-controlled trial is ethical given that 076 provided a standard of care in wealthy nations. Fortunately, in April 1998, this dilemma was resolved. After a trial in Thailand found a short course of ZDV to be effective in reducing mother to child transmission of HIV infection, all placebo arms of ongoing trials were stopped.

## **Conclusions**

It is a striking feature of the global AIDS pandemic that the new combination therapies and the antiretrovirals upon which they are based are virtually unavailable where the disease poses the greatest threat. This situation is, of course, not dissimilar to the more general pattern that prevails in medicine, but it is unique in that it is within recent memory that the advanced industrial world shared with the most impoverished nations a common fate of relative therapeutic impotence in the face of HIV infection.


Given the current cost of the new drug therapies, there is little likelihood that they will become widely available where they are so desperately needed. And, indeed, given the relative importance of prevention in nations where the incidence of infection is still alarmingly high, it is unclear, even were ARVs marginally more affordable, that investment in such therapeutic agents would be a wise use of resources. This state of affairs is a consequence of deep and widening gulfs in wealth between and within countries, a profound inequality that should fuel our moral concern. It also underscores the importance, despite recent advances in therapeutics, of a continued commitment to the development of vaccines that are inexpensive and easy to administer. Only such a vaccine will meet the needs and moral claims of the poorest nations for effective AIDS prevention. Those claims will be harder to press if, because of antiretroviral therapies, HIV disease becomes a more manageable and less threatening disease in the richest nations of the

world. Many tens of millions of individuals will still be at risk of an infection which for them remains lethal. For this reason, continued and reinforced effort to prevent HIV infection remains an ethical and public health imperative.

### **Further Reading**

1. Bangsberg D, Tulskey JP, Hecht FM, et al. Protease inhibitors in the homeless. *Journal of the American Medical Association* 1997; 278:63-65.
2. Bayer R and Stryker J. Ethical challenges posed by clinical progress in AIDS. *American Journal of Public Health*, 1997, October.
3. Brody B. Public goods and fair prices: Balancing technological innovation with social well being. *Hastings Centre Report* 1996; 26:5-11.
4. Deeks SG, Smith M, Holodny M, et al. HIV-1 protease inhibitors: A review for clinicians. *Journal of the American Medical Association* 1997; 277:145-153.
5. Levine RJ. "International Codes and Guidelines for Research Ethics: A Critical Appraisal" in Vanderpool, Hy (ed) *The Ethics of Research Involving Human Subjects: Facing the 21st Century*. (Frederich, Maryland: University Publishing Group, Inc., 1996).
6. Shue H. *Basic Rights: Subsistence, Affluence and U.S. Foreign Policy*, 2nd ed. (Princeton, New Jersey: Princeton University Press, 1996).
7. Floyd K and Gilks G. Cost and financing aspects of providing antiretroviral therapy in *The implications of antiretroviral therapy*, Van Praag E, Fernyak, S and Martin Katz A. World Health Organization, Geneva, 1997.
8. Van Praag E, Perriens JH. Caring for patients with HIV and AIDS in middle-income countries. *British Medical Journal*, 1996; 313: 440





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

For orders, contact: UNAIDS Information Centre  
email: [UNAIDS@UNAIDS.ORG](mailto:UNAIDS@UNAIDS.ORG)

Office of AIDS and Sexually Transmitted Diseases (ASD)  
World Health Organization

20 Ave Appia - CH-1211 Geneva 27

Tel: 41 22 791 4613 / Fax: 41 22 791 4834

For orders, contact Distribution and Sales at WHO:  
Fax: 41 22 791 4857 / email: [publications@who.ch](mailto:publications@who.ch)