The implications of antiretroviral treatments

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Cover

The design is based on an early Cretan symbol, the Mykenae Spiral dating from 1900 B.C.

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The views expressed in background papers and case presentations by named authors are solely the responsibility of those authors.
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Note for the reader

The aim of this report is to summarize the essential points raised during the consultation and derived from discussions, presentations and background papers.

The informal nature of this multidisciplinary consultation was intended to stimulate discussion, raise issues, clarify state of the art and identify areas of contention in order to define the scope of the implications to be considered in the eventual formulation of policy and guidance. Views expressed in this report do not reflect official policy of WHO or UNAIDS.

Texts of case study presentations and background papers are reproduced in this report in full for readers who wish for further detail.
Background

The consultation was called in response to the recent developments in antiretroviral (ARV) treatments which appear to offer real hope to people living with HIV/AIDS (PLHA) of prolonged and disease free survival. Impressive short-term results have been obtained in clinical trials of combination therapies of three antiretrovirals including one protease inhibitor (PI); and there is evidence of good mid-term clinical results with combination therapies without PIs. Under triple therapy, reduction of viral load in serum to undetectable levels for periods of 12 months and reduction in incidence of opportunistic infections have been observed in some patients, raising the possibility that HIV/AIDS could become a chronic infection, treated primarily on an outpatient basis, thus improving the quality of life for PLHA. People living with HIV/AIDS from all corners of the globe are requesting ARVs and governments are seeking policy guidance on these treatments.

Cautious optimism is still warranted. Long term clinical outcomes 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, strong 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 extremely expensive (US$ 1000-1500 per month) 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, and clinical and laboratory monitoring is required to detect adverse reactions. Drug interactions have to be considered, particularly the potentiating effect of protease inhibitors on rifampicin, a drug used to treat tuberculosis.

The use of ARVs to prevent mother-to-child transmission (MCT) of HIV was shown, as long ago as 1994, to be extremely effective (reducing transmission by nearly 70%) and there is some certainty about the sustainability of these results. Whereas monotherapy for the treatment of HIV infection is now regarded as obsolete because of serious problems of resistance, a short course of monotherapy for prevention of MCT might be effective and would be likely to pose few such problems.

Currently available ARVs are far from ideal but ongoing pharmacological research may produce drugs that are less costly, easier to administer, and pose fewer problems of adverse effects or resistance. Despite these difficulties, triple therapy has become the standard of care in the industrialized countries.

With the new treatments, there is now a stark contrast between the fate of HIV-infected people in the industrialized countries and those in poorer settings. This contrast is all the more troubling as the vast majority of HIV infected people live in the developing countries and more than 60% in sub-Saharan Africa, areas of the world that have been the worst hit by current economic upheavals and where even basic needs for food, water and shelter are not always met. Nevertheless, ARVs are present even in the poorest countries, but are only accessible to a very small, wealthy minority. In these situations, some physicians may be prescribing ARVs without sufficient understanding of correct use. It is therefore urgent for policy makers, ministries of health, and NGOs to address all aspects of ARV treatments including access, irrespective of the wealth and circumstances of their country.
Access to ARV treatments is clearly a major issue for discussion. However, efforts must first be concentrated on establishing the "state of the art" of these treatments. This is a rapidly evolving field and the "best" drugs available today are likely to be superseded in the near future.

Furthermore, given the physical pain and anguish suffered by PLHA, in addition to the enormous expense they may incur in trying to obtain ARVs, it is extremely important not to raise false hopes. In order to ensure responsible policy making, more information is needed on the sustainability of recent successes. All of the above must be weighed against the rights of PLHA to treatments which may not be life saving but which would permit a longer and fuller life. Bearing in mind the above considerations, the aim of the WHO consultation was to:

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

It was not the aim of this consultation to formulate guidance to policy makers but rather to prepare the ground through exploration of all the issues, and examination of the implications of providing ARV treatments in various settings. However, it became clear during the consultation that the formulation of guidance must be an immediate follow-up activity. WHO's Office of AIDS and Sexually Transmitted Diseases is now coordinating the production of a series of guidance modules, to be made available towards the end of 1997.

Participants at the consultation 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.
Antiretroviral drugs: classes, modes of action and indications

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. These agents target enzymes which are important for RNA replication and viral functioning. Once the HIV retrovirus has invaded a macrophage or T-lymphocyte, the enzyme HIV reverse transcriptase converts the viral RNA genome into a DNA copy, which is then integrated into the host chromosome by the enzyme integrase. A third enzyme, protease, contributes to viral functioning by catalyzing the cleavage of virion core proteins for final assembly of viable virions. Once HIV has integrated into the host DNA, the virus multiplies rapidly, creating several billion new copies a day. This inevitably results in mutations of the viral genome and the development of variant strains. Some of the mutations may confer resistance to one specific agent or a whole class of ARVs.

Zidovudine (AZT), the first antiretroviral to be developed, became available in 1987. Other NRTIs were introduced in the early 1990s but it took until 1995 to demonstrate that therapy with two drugs was more effective than with zidovudine alone. Monotherapy with AZT is now regarded by many clinicians and researchers as obsolete for the treatment of HIV infection, but is still used for prevention of mother-to-child transmission. The problem of the development of resistance in mothers who have received multiple doses of AZT, in communities where the drug is much used, is not resolved. Bitherapy to prevent MCT is increasingly being used and might become the standard of care in industrialized countries.

Over the last year, evidence has accumulated showing that a combination of three ARVs, including one PI, is the most effective treatment available to suppress the replication of HIV. This is reflected clinically in decreased incidence of OIs, decreased hospitalizations and ability to return to normal functions of daily living. In laboratory tests, it is reflected in decreased viral loads (often to undetectable levels) and increases in the number of CD4 cells. However it is not known how long these benefits will last.

Although combination therapies allow patients to live more normal lives, they require strict adherence to complicated regimens. Some drugs must be taken with meals, others while fasting; some must be taken precisely at six or eight hourly intervals; one of the drugs (ddI) must be taken alone and another requires refrigeration (see Table 6 in the background paper on Adherence to antiretroviral therapy). Finally, there is the risk of interactions between ARVs and other drugs commonly used for the treatment of HIV related conditions. Managing these various requirements is time consuming and stressful. In an attempt to solve some of these problems, several new drugs which are more potent, have fewer side effects and easier dosing schedules, which are able to cross the blood-brain barrier and which target the integrase enzyme, are currently being developed and tested.

In 1994, the results of ACTG076, the first study of the use of zidovudine during pregnancy were published and showed that mother-to-child transmission of HIV could be decreased by 67% in HIV-positive pregnant women who were AZT naive and had CD4 counts greater than 200. For the women, the regimen involved oral zidovudine for a median of 11 weeks (range 0-26 weeks) during pregnancy, and IV zidovudine administered during labour and delivery. In addition, the new-born received 6 weeks of zidovudine in drops and was not breastfed.

The promising results of ACTG076 have created a demand for increased access to ARVs for pregnant women worldwide. This has led to additional research which strives to identify shorter, simpler and less expensive ARV regimes to reduce MCT. The details of the current ongoing trials
are provided in the background paper Antiretrovirals and their role in preventing mother-to-child transmission of HIV 1. Methods to reduce MCT which do not involve ARVs are also being explored, such as vaginal disinfection, caesarian section rather than vaginal delivery, and formula feeding. Vitamin A and Pokeweed protein are also being investigated as possible MCT preventive agents.

ARVs have also been used for post exposure prophylaxis (PEP). A case control study showed that AZT administered after percutaneous exposure to HIV among health care workers decreased the risk of seroconversion by approximately 79%.

Eleven antiretroviral agents are currently available in different parts of the world. 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. (Registration differs from country to country.)

Table 1

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name**</th>
<th>Class</th>
<th>Unit Dose</th>
<th>Cost: Three Months /US$$***</th>
</tr>
</thead>
<tbody>
<tr>
<td>didanosine (ddI)</td>
<td>Videx</td>
<td>NRTI</td>
<td>100 mg</td>
<td>420-700</td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td>Epivir</td>
<td>NRTI</td>
<td>150 mg</td>
<td>690</td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>Zerit</td>
<td>NRTI</td>
<td>40 mg</td>
<td>700-730</td>
</tr>
<tr>
<td>zalcitabine (ddC)</td>
<td>Hivid</td>
<td>NRTI</td>
<td>0.75 mg</td>
<td>630</td>
</tr>
<tr>
<td>zidovudine (AZT)</td>
<td>Retrovir</td>
<td>NRTI</td>
<td>100 mg</td>
<td>720-860</td>
</tr>
<tr>
<td>indinavir</td>
<td>Crixivan</td>
<td>PI</td>
<td>800 mg</td>
<td>1350</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>Viracept</td>
<td>PI</td>
<td>250 mg</td>
<td>1670</td>
</tr>
<tr>
<td>ritonavir</td>
<td>Norvir</td>
<td>PI</td>
<td>600 mg</td>
<td>2080</td>
</tr>
<tr>
<td>saquinavir</td>
<td>Invirase</td>
<td>PI</td>
<td>600 mg</td>
<td>1720</td>
</tr>
<tr>
<td>delavirdine*</td>
<td>Rescriptor</td>
<td>NNRTI</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td>nevirapine</td>
<td>Viramune</td>
<td>NNRTI</td>
<td>100 mg</td>
<td>740</td>
</tr>
</tbody>
</table>

* delavirdine is only available in ongoing clinical trials
** brand names may vary between countries
*** ranges reflect dosing variations
Current standards of care based on published guidelines

Patients usually develop symptomatic HIV disease, and progress to AIDS approximately seven and ten years after infection, respectively. Disease progression can be monitored clinically and with laboratory tests, through viral load measurement and CD4 cell counts. The risk of dying from AIDS is most strongly correlated with a patient's viral load. A patient with a viral load greater than 30,000 copies/mL is 18 times more likely to die than a patient with a viral load less than 500 copies/mL. Although CD4 counts also correlate with disease progression, the association is weaker than with viral loads. A patient with a CD4 count less than 200/cmm is 4 times more likely to die than a patient with a CD4 count greater than 750/cmm. CD4 counts are most useful for making decisions regarding prophylaxis of opportunistic infections (OIs) and for predicting the onset of OIs. (For a general discussion of these issues see background paper on Treatment of HIV infection: current recommendations for the use of antiretroviral drugs.)

Guidelines for the use of ARVs have been issued in the last year from groups in several countries. Many crucial questions concerning these therapies, such as when to begin, when to stop, when to change drugs, and which drugs to use have still not been clearly answered from ongoing clinical trials. This is especially so for the treatment of asymptomatic HIV infection (with CD4 greater than 500), where clinical benefit of early treatment has not been proven.

The standard of care for the treatment of HIV infection, at the time of the consultation, was double therapy with two NRTIs or triple therapy with two NRTIs and one PI, or two NRTIs and one NNRTI. It should be noted that data on the use of PIs as initial therapy in early disease is limited. In France, 52% of patients are on a double nucleoside regimen, and 43% are on a triple regimen including one protease inhibitor. In Brazil, bitherapy is recommended for the majority of patients. The most aggressive guidelines treat HIV disease, symptomatic or asymptomatic with CD4 less than 500 and/or viral loads greater than 5-10,000 copies/mL. For asymptomatic patients with CD4 counts greater than 500/cmm, therapy is recommended when the viral load is greater than 30-50,000 copies/mL and should be considered when greater than 5-10,000 copies/mL.

Viral load is monitored every 3-4 months and changes are made in the treatment regime when the viral load increases or the patient no longer tolerates the combination therapy. In addition, complete blood count, liver function tests, amylase and electrolytes are performed every 3-4 months to monitor for adverse reactions. For patients considering initiating ARV treatment, viral load is measured every 6 months.

In current practice, treatment is changed when it fails, when there are adverse reactions, or when drug interactions make its continuation problematic. The proposed virological criterion for treatment failure is viral load greater than 5-10,000 copies/mL or less than 5-10,000 copies/mL, but rising. When PIs are used, it may take 16-20 weeks to reach maximum antiviral effect. "Failure" may be due to several factors, including incomplete suppression of HIV replication, progression of immunological decline, drug interactions, non-adherence, and stimulation of virus replication (due to concurrent viral or bacterial infection).

Unresolved issues

There are conflicting views on the use of ARVs in settings which may not have the resources to perform frequent viral loads or provide bi- and triple therapy. For some, the primary goal is to provide ARVs, whether or not viral load, and/or changes in CD4 cell counts, can be monitored. The treatment may be monotherapy with a NRTI, irrespective of concerns regarding the almost certain development of resistance. This may allow a small increase in survival and quality of life
and perhaps time to "deal" with the disease and die with dignity. Some feel that if any gain in survival or quality of life, no matter how small, is possible, the treatment should be made available to all infected with HIV. This position is unacceptable to those who are concerned about the development of resistance, and consequently the reduced effectiveness of therapy now and in the future.

An alternative suggested at the consultation would be to provide bi- or triple therapy without viral load monitoring to symptomatic patients and patients with AIDS, using clinical signs as a measure of the adequacy of therapy and basic laboratory tests to monitor for toxicity. Some argue that development of clinical signs will most certainly indicate that resistance has already developed, and it will be "too late" to halt this process. Others point out that likewise, once viral load begins to rise, resistance may already have occurred and it is also "too late". This is clearly an area which requires further investigation and discussion in order to reach an agreement that respects both the individual's desire to access treatment and the public health responsibility to minimize the development of resistance.

Post exposure prophylaxis (PEP): guidelines from the US Centers for Disease Control

Guidelines for the use of ARVs to decrease seroconversion following occupational exposure have been developed by the Centers for Disease Control (CDC), based on expert opinion. It should be noted however, that data on the efficacy of ARVs in PEP and on the toxicity of ARVs in non-infected individuals is extremely limited, and that the average risk of seroconversion following percutaneous exposure is very low (0.3%).

For those at highest risk (large volume of blood and/or high titre of HIV in source patient) ZDV, 3TC and indinavir may be recommended; for middle risk, ZDV and 3TC and for lowest risk, ZDV with or without 3TC may be offered. (See MMWR Vol 45, No. 22, June 7 1996, pages 468-472 for complete recommendations.)

In all cases PEP should be initiated 1-2 hours following probable exposure of an HIV-negative health worker and administered for 4 weeks, if tolerated. Health care workers should receive follow-up counselling and medical evaluation, including HIV tests at baseline, 6 weeks, 12 weeks and 6 months. In addition, counselling should include information on the necessary precautions to prevent possible secondary transmission. Adverse reactions should be monitored serologically at baseline and 2 weeks following initiation of therapy.
Issues for the individual

The perspective of people living with HIV/AIDS

For many PLHA, ARVs represent the only hope and the best available treatment, which while not life saving, may increase survival and quality of life. A chronic illness requiring mostly outpatient care is a very different prospect from a disease which - once it develops - causes much suffering and is rapidly fatal (6 months to 2 years). Understandably, for PLHA, obtaining these drugs is an imperative.

For the majority of PLHA, the difficult regimen and unpleasant side effects are aspects which must be tolerated in order to reap the benefits of the treatment. It is increasingly recognized that clinicians and other health providers, as well as the PLHA him or herself, have responsibilities in facilitating adherence. For some PLHA, unpleasant side effects may be severe enough for them to decide to stop treatment.

Quality of life on ARVs can best be assessed by the individual under treatment. Assessments may vary considerably as people react very differently to discomfort, stress and inconvenience. For asymptomatic PLHA, the decision is particularly difficult, as they may be leading completely ‘healthy’ lives. Introducing ARVs may transform a healthy life into one which is dominated by the effort required to manage a complicated regimen and made less agreeable by unpleasant side effects.

Obtaining ARVs “whatever the cost” is likely to be the major preoccupation of many PLHA who are aware that the treatment exists and is being provided at no or little cost to all PLHA in industrialized and some middle income countries. Governments are sometimes seen as having an obligation to provide ARVs by whatever means to all those in need. Whilst policy makers must weigh this option against other more cost effective interventions which address public health priorities in general, it would be inappropriate and unrealistic to expect PLHA to do so.

Past experience shows that drug prices do come down; the people concerned often have to lobby and fight, ask for help, and demand that their rights to treatment be respected. Many PLHA and those working with them feel that providing ARVs is a question of political will. They point out that HIV/AIDS activists have already set precedents in the past in challenging established procedures regarding access to treatment, and are likely to do so again in relation to the new therapies.

Risks and benefits of treatment

For the individual patient, the decision to begin ARV treatment requires careful consideration of a number of issues and thorough discussion with his or her physician. Benefits of therapy may include:

- a longer life
- control of viral replication
- development of fewer drug resistant mutations, particularly when adherent to triple therapy
- prevention of immune deficiency
- delayed clinical progression of disease, fewer opportunistic infections
- decreased risk of transmission.
Potential disadvantages include:

- impairment of quality of life because of the difficult regimen or unpleasant side effects.
- early development of drug resistance and cross resistance, when ARVs are not effective, limiting the number of available therapeutic options in the future, and increasing the risk of transmission of resistant strains.
- raising false hopes of therapeutic gain in a proportion of patients who will either not respond or not tolerate the therapies.

Adverse reactions to ARVs and interactions between ARVs and other drugs commonly used to treat HIV-related illnesses are listed in Table 2. It should be noted that long term toxicities, particularly with respect to children who have received AZT in utero and post-natally are not known. Of particular concern are interactions with drugs for concurrent TB infection. Patients on rifampin or rifabutin for the treatment of TB, in general, should not continue or begin treatment with PIs (see background paper on Adherence to Antiretroviral Therapy for treatment options).

Table 2*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse reactions</th>
<th>Drug-drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>delvaridine</td>
<td>rash, abnormal LFTs</td>
<td>rifampicin, rifabutin, ddl, antacids, anti-epileptics, PIs</td>
</tr>
<tr>
<td>didanosine (ddl)</td>
<td>pancreatitis, peripheral neuropathy, nausea/vomiting, diarrhoea</td>
<td>fluoroquinolones, dapsone, isoniazid, itraconazole, ketoconazole, tetracyclines</td>
</tr>
<tr>
<td>indinavir</td>
<td>hyperbilirubinemia, nephrolithiasis</td>
<td>rifabutin, rifampicin, cisapride, terfenadine, astemizole, warfarin</td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td>nausea/vomiting, pancreatitis</td>
<td></td>
</tr>
<tr>
<td>nelfinavir</td>
<td>diarrhoea</td>
<td></td>
</tr>
<tr>
<td>nevirapine</td>
<td>rash, Stevens-Johnson syndrome, abnormal LFTs**</td>
<td>PIs, rifabutin, rifampicin, indinavir</td>
</tr>
<tr>
<td>ritonavir</td>
<td>nausea/vomiting, diarrhoea, hypertriglyceridemia, abnormal LFTs, peripheral neuropathy, perioral paraesthesia, headache</td>
<td>alprazolam, clarithromycin, diazepam, erythromycin, ketoconazole, itraconazole, rifabutin, saquinavir, tricyclic antidepressants, oral contraceptives</td>
</tr>
<tr>
<td>saquinavir</td>
<td>severe hepatic impairment, diarrhoea, nausea, abdominal pain</td>
<td>ketoconazole, rifampicin, rifabutin, phenytoin, carbamazepin</td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>peripheral neuropathy, pancreatitis, anemia, neutropenia, headache, nausea</td>
<td></td>
</tr>
<tr>
<td>zalcitabine (ddC)</td>
<td>peripheral neuropathy, pancreatitis, stomatitis</td>
<td>warfarin</td>
</tr>
<tr>
<td>zidovudine (AZT, ZDV)</td>
<td>anemia, neutropenia, headache nausea</td>
<td></td>
</tr>
</tbody>
</table>

* NOTE: This table is not exhaustive.
** Liver Function Tests
Resistance

The rapid replication rate of the HIV virus, coupled with the many errors made by HIV's reverse transcriptase enzyme in copying the HIV genome, produces many mutations of the HIV virus. These mutations may result in changes in the protease and reverse transcriptase enzymes, so they are no longer inhibited by ARV agents. In the presence of antiretroviral agents, these variants may be amplified, resulting in drug resistant strains. In vitro studies suggest that resistance to zidovudine develops in approximately six months, although clinical evidence of resistance may take up to two years to appear. Resistant strains emerge at varying rates with other NRTIs. However, resistance to NNRTIs and PIs can develop over the course of weeks if they are used intermittently or as monotherapy. A recent, small study observed rapid rises in HIV RNA after a few days of missed doses of saquinavir taken as monotherapy and a possible association with the emergence of resistant strains. Within the class of PIs, there is often cross-resistance between different compounds. (See background paper on Resistance to antiretroviral drugs for further details on this subject)

When AZT is used as monotherapy, evidence suggests that HIV drug resistance is probably causally associated with treatment failure and death. When a patient is able to adhere to the rigorous schedule needed to take triple therapies, viral replication may be suppressed, limiting the opportunity for the virus to develop resistant strains. Unfortunately, clinical practice suggests that this may only be achievable in a proportion of patients. In addition, there are strong theoretical reasons to expect that sub-optimal serum concentrations of ARVs, due to poor adherence, drug-drug interactions or viral stimulation, will lead to a more rapid development of resistance. Data on this issue are expected to be published soon.

Although drug resistance will develop in those individuals who are on AZT monotherapy for six months to two years, resistance is less likely to develop when it is used for shorter periods of time to decrease mother-to-child transmission of the virus. Consultation participants suggested that in order to maintain the effectiveness of zidovudine monotherapy in decreasing mother-to-child transmission of the virus in a particular community:

- women should receive short course monotherapy with zidovudine during the perinatal period;
- between pregnancies women should be offered bi- or triple ARV therapy or no therapy - monotherapy is not an option;
- monotherapy should be discouraged in the community at large, to reduce the likelihood that zidovudine resistant strains of HIV will be transmitted to women of child-bearing age.

These standards are crucial for limiting the emergence of drug resistance. If ARVs are not used responsibly, women will acquire AZT resistant virus and transmit it to their children and partners. This limits future treatment options for all members of the community. In addition, the issue of viral rebound in women who stop AZT following pregnancy has not been adequately addressed for many settings. It was suggested, although there are no data to support it, that women may risk accelerating their own disease progression when taking ARVs as monotherapy to reduce MCT, for limited periods during several pregnancies.

Adherence

Given the complicated dosing schedules for antiretroviral agents, the constant threat of the development of resistance and the immense cost of the therapies, adherence to the regimen is essential. In general, adherence to medical regimens is poor, with published literature suggesting
rates as low as 50% for treatment of many diseases. There is little data on adherence in HIV
disease, and virtually no data on adherence with respect to bi- and triple therapy combinations of
ARVs. One careful prospective study of adherence to zidovudine monotherapy, outside of a trial
setting, reported that only 26% of patients were correctly using their medications at six months.
Anecdotal reports are not useful as most clinicians assume a high rate of adherence in their
patients, which is not borne out by studies in which patients are directly questioned.

Despite these sobering statistics, there are ways in which patient adherence can be improved.
A key factor is the patient-clinician relationship. The decision to begin ARVs should be
approached openly by the clinician and the drugs should be offered equally to all patients.
Treatment decisions should be made jointly between the patient and the clinician after careful
discussion of the pros and cons of treatment, treatment options, possible adverse reactions,
necessity for adherence and the long term emotional (and often financial) commitment that one
must make to successfully use ARVs. This is clearly very difficult in many clinical settings where
clinicians often have only a few minutes to spend with each patient.

When the decision has been taken by the patient and clinician to start ARVs, additional
psychosocial support to help maintain adherence to the regimen, needs to be organized. This may
include material support organized by social services, NGOs or community groups, counselling,
emotional support from partner(s), family, and friends - as well as easy and confidential access to a
clinical setting and care provider to deal with any concerns and for routine follow-up. In many
settings, this level of care and social support is not yet developed.

In the development of new drugs, issues which make adherence easier should be addressed,
such as minimal adverse reactions to the medication, fewer drugs and tablets each day, less
frequent dosings, and little disruption to one’s lifestyle.
Issues relating to the provision of health care

Integrating ARVs into the health system

Whether or not ARVs are incorporated into existing structures or provided in special centres, the organization of services should ensure, at the least, sustainable supplies, trained providers, basic laboratory facilities for monitoring toxicity, regular clinical follow-up, and psychosocial support to reinforce adherence.

The organization of such services is best achieved as part of the provision of a continuum of care from the home, through local health centres and support groups to referral centres. At each of these levels, a range of clinical, social, counselling and nursing needs of the PLHA can be addressed at different times. PLHA have a wide variety of needs and variable access to services. Coping and acceptance is a long and difficult process. Illness progresses irregularly and there may be long periods of good health when no medical services are required; however medicines will still need to be taken. Even when patients progress to AIDS, there will be times when they are better cared for at home by a partner or the family with a care provider as appropriate. In order that various health and social needs be met, discharge planning and referral between levels must be functional, flexible and prompt.

Information and education about ARV treatments, if these are available, are part of the comprehensive care of PLHA. Clear, practical information about the pros and cons of the treatments themselves in the particular circumstances of each individual patient, must be offered as well as information about where and when to access additional support and care.

A number of questions remain. Should specific management programmes be developed to deliver ARVs, similar to the vertical programmes currently in place for the treatment of tuberculosis? Should new treatment units and laboratory facilities be established specializing in ARV treatments, or should ARV treatments be incorporated into current facilities? If so, should these be limited to specialized settings which already have in place the necessary laboratory facilities and trained clinicians? Should they be limited to patients in a functioning social support network? How can quality and accurate record keeping and follow-up systems of care be assured and maintained?

Training of health professionals

The importance of training clinicians in the specifics of ARV management cannot be overemphasized. Clinicians should have up-to-date knowledge about the available bi- and triple therapy regimes and monotherapy to decrease MCT, their pros and cons, appropriate dosing schedules, drug-drug interactions, possible adverse reactions, and the appropriate monitoring (using both clinical and laboratory indicators) of patients on ARVs. In addition, they should be comfortable sharing decision making with the patient, including providing accurate information on ARVs. In some settings, only HIV specialists or other clinicians trained specifically in the safe and effective use of ARVs may prescribe and care for patients on these regimens. However in countries with many patients and few resources this may not be feasible. Thus, training courses for different health professionals will need to be designed and the decision made as to who will be allowed to prescribe ARVs - specialists only, or general practitioners who have undergone appropriate training.

Voluntary counselling and testing

Voluntary and confidential counselling and testing (VCT) services must be available and affordable so that those who may benefit from ARV treatments can present for testing to determine
their HIV status. VCT services should be accessible, and provide pre- and post-test counselling. They should have access to a laboratory with a reliable supply of tests for the diagnosis of HIV infection (at least two different ELISAs), and of laboratory reagents and supplies, as well as a technician trained to perform HIV tests correctly. A quality control programme should be in place to ensure consistent and reliable results. In addition, health workers need to be trained to provide adequate pre- and post-test counselling for those seeking testing.

The advantages of learning one’s HIV status include not only earlier access to care, but also the possibility of modifying one’s behaviour to decrease the risk of spreading infection, drawing on others for needed psychosocial support, and using the information to plan more appropriately for the future. If ARV use becomes more widespread and the clinical benefits of treatment are perceived to be high, there will most certainly be greater demand for VCT. This will clearly be a burden on the current health system, which in some areas of high HIV prevalence is already unable to meet demands for VCT services. (See background paper on The implications of antiretroviral therapy for voluntary counselling and testing for more details on this subject.)

**Laboratory support**

Laboratories should be staffed with trained workers and have appropriate and adequate supplies to diagnose common opportunistic infections such as common bacterial pneumonia, tuberculosis, salmonellosis, cryptosporidiosis, candidiasis and cryptococcosis. The staff should be adequately trained and the facilities equipped to monitor for adverse drug reactions using complete blood counts, liver and renal function tests, and amylase tests.

In addition, the ability to readily and accurately perform CD4 counts and viral loads may be necessary for some subsets of patients. In the industrialized world these tests are being performed in specialized centres. The most automated and reliable method for determining CD4 count is the “fluorescent activated cell sorter”. Less expensive, less accurate and more labour intensive methods exist and are described in the background paper on Laboratory requirements for antiretroviral treatments.

The running of viral load assays involves the use of kits which employ either polymerase chain reactions, branched DNA signal amplification or isothermic nucleic amplification to quantify HIV and can be obtained from the manufacturers for approximately US$ 100/test. The currently available kits are most efficient at amplifying HIV-1B, less efficient at amplifying other HIV-1 subtypes and are not able to detect HIV-2 and HIV-0. Each of the these assays requires different procedures and laboratory facilities, and expensive equipment.

Specific drug resistance can be determined using genotypic assays. Currently in the industrialized world, these require a laboratory equipped to perform nucleic acid sequencing. Individual tests require US$ 20 in reagents and take three days to run. Increasing viral loads and decreasing CD4 counts may also indicate the onset of drug resistance. However, without assays, the specific culprit cannot be identified.

Properly equipped laboratories are clearly expensive. Additional costs which must be considered include laboratory infrastructure, annual overheads, and staff training which should be undertaken every two years. These costs vary considerably between countries and precise estimates cannot be made here. Costs of certain items such as diagnostic tests may decrease with time. In order to share these costs, several institutions can pool their resources to create a central laboratory. In addition, opportunities to collaborate with outside institutions may exist.
Clinical and laboratory guidelines

Health professionals cannot responsibly and confidently prescribe new treatments with complicated regimens and serious side effects without guidelines. These will have to be regularly updated as regimens and agents currently recommended may be obsolete within a very short period of time. Guidelines are starting to be produced in a number of countries. Other countries may wish to use these as a model, or convene expert technical working groups to develop guidelines tailored to the needs of the specific setting.

As very strong commitment is required of the patient, clinician and the health system to make these regimens effective, benefit from their use needs to be clearly demonstrated. Protocols to monitor the use of these treatments may therefore need to be designed to answer the following questions:

- Are quality drugs and services being provided?
- Are patients able to adhere to the rigorous dosing schedules demanded by these therapies?
- Are ARVs improving the overall health of those living with HIV/AIDS? At what cost?
- Are they making a measurable difference to the survival and quality of life of patients taking them? Or do the numerous adverse reactions cancel out the benefits?
- Is there evidence that drug resistance is developing in the community of PHLA who are taking ARVs?
- What is the impact of the ARV policy which is adopted on the use, cost and outcome of HIV service provision: hospital bed utilization, outpatient care and AIDS deaths?

Mother-to-child transmission (MCT)

One of the most cost effective uses of ARVs to date is in the reduction of mother-to-child transmission of HIV infection. Unfortunately, the successful integration of this intervention into health services is beset with difficulties. In some parts of the world, only 60% of women receive prenatal care, 40% have a trained assistant present during delivery and 30% deliver in institutions. In these situations, the use of the ACTG076 protocol (see earlier section on antiretroviral drugs) is not an option. Shorter treatment courses applicable in such settings are currently being evaluated in clinical trials.

The identification of an effective and simple regime does not assure its successful use. In order to inform patients of possible choices, voluntary counselling and testing (VCT) should be available so that those who wish to do so may learn of their HIV status. VCT includes cheap, quick and accurate tests coupled with appropriate counselling services. Counsellors should be trained to discuss issues that are specific to women and pregnancy. Careful thought should be given to whether it is in the woman's best interest to learn her HIV status. If no ARV treatment can be offered to those found HIV-positive, is knowledge of serostatus helpful? The advantages in terms of adopting protective measures need to be weighed against the risk of negative consequences such as being abandoned by husband and family.

The decision to undergo testing and/or start preventive treatment is one that only the woman herself can make and it should be made in an environment which provides factual information and psychosocial support. ARVs cannot be provided to pregnant women if appropriate prenatal care is not available. This means health services which are willing to accept and care for women infected with HIV, and clinicians who are trained in the use of ARVs during pregnancy and have a thorough understanding of adherence, resistance and monitoring for adverse reactions.
Finally, it is important to consider other simple but vital services which should be in place: equipment and facilities such as gloves, clean needles and disinfectants, and functioning delivery units; cheap and simple medical practices to reduce MCT, such as minimizing the use of episiotomy, artificial rupture of the membranes, vacuum extraction and other methods of assisted delivery, and vigorous nasogastric suctioning of the newborn; wiping bloody secretions from the neonate, and providing advice about cracked nipples during breastfeeding. Alternatives to long term breastfeeding should be explored including not breastfeeding or breastfeeding only during the early months of life (on condition that formula milk can be provided safely), and providing AZT drops to breastfed babies. (See background paper on Antiretrovirals and their role in preventing mother-to-child transmission of HIV-1 infection for more details on this subject.)
Societal and public health issues

Priority setting

The decision to introduce ARVs into a public health system comes at the end of a long process of priority setting at different budget levels within a country. At the highest level, are government decisions regarding budget allocations to different sectors, such as education, national defense, employment and health. The setting of the national budget is largely outside the scope of this discussion although it should be noted that certain activities in sectors other than health may receive funds for HIV/AIDS prevention work, notably education, (for example for sex education in schools). Other sectors may also undertake activities which have a significant public health impact, for example, provision of clean water and sanitation by ministries of public works. The provision of ARVs will have to be weighed against interventions such as these, in the interests of allocating scarce resources towards activities which contribute most to overall development.

Once the level of the health budget is set, prioritizing amongst all health interventions needs to be undertaken. At this level, epidemiological assessment of the magnitude of ill health due to HIV/AIDS relative to other conditions is required. Estimates indicate that other health problems are currently of greater magnitude than HIV/AIDS on a global level although this pattern is changing. HIV/AIDS currently ranks as the 26th leading cause of years of healthy life lost, but it is estimated that it will rank 10th in the year 2020. Policy makers need to determine the difference that ARV treatments could make to improving overall health, and this depends on the relative contribution of HIV/AIDS to ill health in specific countries.

Prioritizing amongst budget needs for all HIV/AIDS activities occurs next. It is at this point that cost effectiveness of ARV treatments in terms of reducing the burden of disease needs to be compared to all other HIV/AIDS interventions. Preventing new infections through the promotion of safe sex, particularly the use of condoms, or controlling STDs, may be found to be more cost effective than providing ARV treatments. Care and prevention activities may also have to compete with research activities to develop better interventions for the future. It may justifiably be argued for example that the public health interest in a vaccine or microbicide makes it imperative that resources not be diverted at this point towards very costly drugs, the long term benefits of which remain to be proven.

Finally, priorities need to be set within the various indications for ARV treatments (PEP, MCT, treatment of symptomatic and asymptomatic HIV infection) and among the different treatment options, bitherapy, triple therapy in their various combinations, and for different target groups. In resource constrained settings the best case scenario for provision of ARVs would be targeted use and closely monitored groups: in the worst case scenario, haphazard use would be determined largely by ability to pay. Furthermore, insufficiently supervised treatment, would not improve survival, but would rather enhance resistance, undermine prevention efforts and be a useless drain on resources. (See background paper on Setting priorities for government involvement with antiretrovirals for more details on this subject.)

Allocation of ARV treatments

Given the enormous resources required to provide and properly use these drugs, it is likely that in many settings, the only indications for ARVs which can realistically be considered by the public sector are the prevention of mother-to-child transmission and/or post exposure prophylaxis for health workers. There may be settings with high prevalence and few resources, where no ARVs can be provided by the public sector at all, at least in the short term.
In settings with more resources, some or all of the various options may be considered. Decision makers may have to prioritize among the subsets of the population to be covered (e.g. pregnant women, health care workers (PEP), symptomatic AIDS, symptomatic and asymptomatic HIV infection) and the treatment regimes which will be offered to these groups. The size of different subpopulations has major implications for the total cost of treatment, as well as its potential for reducing the burden of HIV/AIDS. Clearly, if only health workers are provided with post-exposure prophylaxis in the event of an accidental injury, the size of the population to be treated with ARVs will be extremely small. If all HIV positive pregnant women are prescribed a short course of monotherapy, the numbers treated may be greater. Depending on both prevalence and GNP, the treatment of all HIV infected people, symptomatic and asymptomatic may be affordable or, in the case of most developing countries, prohibitive - absorbing many times the overall health budget of the country.

Affordability, sustainability and financing

The cost of ARV treatments is the most obvious and apparently insurmountable barrier to their wide accessibility. It includes not only the cost of the drugs themselves but also the cost of providing supportive health and social services essential for safe use and adherence, the setting up or strengthening of treatment units, laboratory facilities, drug delivery systems and training of health professionals.

Estimates of the annual cost of providing ARVs to all HIV infected people as a percentage of GNP, health sector expenditures and national AIDS budgets (see Table 4 in the paper on Cost and financing aspects of providing ARV therapy), show that even in the wealthiest countries, universal coverage implies expenditures which sometimes exceed the entire HIV/AIDS budget. In many sub-Saharan Africa countries, such coverage implies expenditure 20 times the level of the entire budget for health.

Although it can be expected that the price of ARVs will come down, innovative mechanisms which may challenge established procedures will have to be devised and promoted in public and private sectors. Negotiations with industry have already started and must continue. Strategies for reducing prices include: at national policy level - exemption from taxes and price regulation; through the market - generic competition and drug donations; and through procurement management - preferential pricing, bulk purchase and procurement guarantees.

Part of the cost of the drugs may be offset by savings due to improved health on combination therapy - decreases in the incidence of opportunistic infections and in hospitalizations. Additionally, as combination therapy may offer the possibility to some of returning to work, it may be argued that the cost of the drugs can be partly offset by regained productivity. The real costs and benefits, to society as a whole, of providing ARVs, need to be studied but the assessment of these must recognize the value and quality of each individual life rather than simply “measurable” elements such as lost productivity.

Issues of drug registration and distribution

The guiding principle of the drug regulatory process is the assurance of drug quality, efficacy and safety. The development of resistant microorganisms to any drug or class of drugs is a key factor requiring assessment in this process. In the case of ARVs, this issue is critical, for several reasons: firstly, the development of resistant strains of the HIV virus is rapid; secondly, the currently available ARVs are extremely expensive, so it is essential that they not be used when they have become ineffective; and thirdly, when adherence is poor and benefit shortlived, the only effect of their use may be to produce and spread more resistant strains.
Regulatory authorities rely on data supplied by the manufacturer but they may also conduct independent tests especially to validate content and drug concentration (quality). This is rarely the case in developing countries where the necessary laboratory resources are not available. Given the distribution of different strains of the virus in different regions of the world, this is an unsatisfactory situation. It will become increasingly important to develop local laboratory and research infrastructure and to run clinical trials locally in order to understand the pathogenesis of local viral strains and the emergence of drug resistance.

The importance of providing information to patients about adherence cannot be overemphasized and is a responsibility shared by clinicians, regulatory authorities and manufacturers. Policy makers need to bear in mind that in situations where patients must pay for treatment themselves, the cost of therapy as well as the side effects of drugs may contribute to non-adherence.

Drug regulatory agencies are under pressure to assess and approve newer antiretrovirals more quickly. A “fast track” procedure can be justified on the grounds that the disease is fatal and no known cure exists. Nonetheless, such a procedure should take into consideration adverse reactions to ARV drugs and quality of life under treatment.

With regard to developing country drug regulatory capacity, it should be borne in mind that established procedures for introducing new drugs exist. If these are inadequate they should be strengthened rather than bypassed. Weak points in the system need to be identified and addressed, notably quality control and the black market in drugs. Finally, some developing countries are already producing ARVs and others have the capacity to do so, which highlights the need to strengthen and monitor quality control and distribution procedures.

**Ethical issues**

The significant advances in therapeutic efficacy of the new combination therapies have introduced new challenges into an area which was already sensitive and “highly charged” with ethical questions. For as long as no effective treatment existed for HIV/AIDS, there seemed to be a broad consensus on the ethical questions of avoiding discrimination and ostracism, respecting confidentiality, and ensuring voluntary testing and counselling.

With the recent introduction of what appear to be significantly more effective therapies, the range of ethical issues requiring consideration includes the two following broad areas:

- equity and justice in relation to access to treatments; and,
- the extent to which governments may limit individual liberty in the interests of public health.

In addition, ethical issues relating to specific groups and contexts are raised by particular indications for ARVs such as the prevention of mother-to-child transmission and post-exposure prophylaxis for health workers.

**Equity and justice**

Price is at the centre of the question of equity and justice. Whilst attention has been paid to distributive justice once prices have been fixed, there has been little consideration of the ethics of pricing itself. Given the prohibitive cost of the new combination therapies, it may justly be stated that the time has come to broaden the scope of discussion and assert that the market is not the only mechanism for determining the “right” let alone the “fair” price of drugs.
Few would support the idea that ability to pay should determine access - even if in practice, it frequently does. There are three other principles upon which to base rationing of treatments when this appears inevitable: 1) “first come first served”; 2) relative merit - which in practice favours older people and those who are already privileged; and 3) utility, which favours those regarded as most useful to society - generally the young and productive. Another principle states that no treatment should be available to anyone if it is not generally available. At face value this position appears to have some validity but from the humane and practical point of view, it would seem more reasonable to “start somewhere”, and tolerate a degree of injustice, especially since even the most rigid interpretation of this principle will not prevent ARVs being present in countries and obtained by the most wealthy.

In a number of rich and middle income countries, there will be no need to debate these issues, as all those in need will receive treatment. However, unless positive action to ration treatments on the basis of one or other of these principles is taken, ability to pay is likely to determine access in many settings. It is to be hoped that principles of universal access and solidarity between rich and poor within and between nations will encourage the establishment of mechanisms to increase access to those in need.

*Individual liberty versus public health interest*

Problems of adherence to difficult drug regimens and the consequent increased risk of emergence and spread of resistant strains raise some very difficult questions about the rights of individuals to treatment and the responsibility of physicians and policy makers to protect public health. Certain groups such as the homeless, the mentally ill or injecting drug users may have difficulty adhering to complicated regimens. Undeniably, their lives may be far too chaotic to permit adherence, and the immediate and only result of starting such patients on ARVs is the development and spread of resistant strains. However, it is not the exclusive responsibility of vulnerable groups themselves to make their lives less chaotic and in turn, to make adherence feasible. Poverty, homelessness, unemployment and medical neglect are structural features of many societies today which are way beyond the control of the vulnerable groups whose lives are blighted by these problems.

A balance has to be struck between providing a supportive and safe environment in which adherence is possible and individual capacity and willingness to lead a more ordered life. Decisions can only be made on a case by case basis and the clinician and patient together need to assess the possibilities of adherence and come to an agreement about treatment. The public health claims in this instance are very strong indeed as ARVs require better than average adherence and the consequence of non-adherence is extremely serious - the spread of non-treatable strains of HIV.

Voluntarism as opposed to coercion in relation to testing, treatment or prevention in HIV/AIDS may be questioned in the light of new possibilities offered by ARV treatments. It has been persuasively argued that coercive measures are counterproductive; they tend to drive the problem underground, and discourage people from presenting for testing, care or treatment, thereby removing excellent opportunities for prevention activities. However, if it is conclusively demonstrated that ARV treatments reduce viral load to the extent that HIV-infected people no longer transmit the virus, there may well be calls for mandatory testing and treatment to halt the spread of the disease.
The example of Directly Observed Therapy (DOT) for tuberculosis is frequently invoked to justify a similar approach with HIV/AIDS, but there are important differences. ARV therapy, unlike TB therapy, is neither curative, nor easy to manage nor monitor. If easier-to-take, curative drugs become available, the argument might become more compelling. However, we should beware of abandoning deeply held principles in our haste to exploit technological advances. Any consideration of such measures must thoroughly assess the cost in terms of losing public confidence, discouraging open attitudes and discussion, and creating the potential for abuse of human rights.

Special groups and contexts

Post exposure prophylaxis (PEP) for health workers has raised a number of interesting ethical questions. Some have argued that PEP for health workers represents a form of privileged access to treatments not generally available to the rest of the population. However, some see such “privilege” as justifiable on the grounds of reciprocity. Health workers caring for HIV infected patients put themselves at a certain risk. In return they should be offered guarantees of the best protection available. Fears of contamination may reduce health workers’ willingness to care for HIV patients and it is very much in the interest of health authorities to keep skilled personnel, especially in high prevalence countries where staff are already being lost to HIV/AIDS (through sexual not nosocomial transmission).

It was argued that following an injury, if PEP fails and the health worker does become HIV-positive, he or she cannot justifiably claim continued therapy (unless this is available universally) as this would favour those infected nosocomially over those infected sexually or through blood transfusion.

The use of ARVs to prevent mother-to-child transmission (MCT) has also posed some difficult questions. This is an intervention that has shown high efficacy (reducing transmission by nearly 70%) and there have been calls for mandatory testing and treatment of pregnant women. There are legitimate concerns about women being treated as “vessels” for their children and about respecting the right of individuals to refuse treatments. These concerns need to be weighed against the right of the child to a healthy life. In the case of MCT, the limited duration of treatment and manageable cost, would appear to justify a short course of ARVs during the third trimester of pregnancy, although there are still gaps in our knowledge about the effectiveness and long term implications of such treatment. Patients’ rights to up-to-date information about the pros and cons of treatments and the right to decide for themselves, remain guiding principles. (See background paper on Ethical challenges posed by the new advances in antiretroviral treatments for HIV disease for more details on this subject.)
Conclusions

The informal nature of the consultation with its array of varying viewpoints, while facilitating important points of consensus, allowed real concerns and differences to surface.

There was a shared understanding that these drugs can improve the life prospects of PLHA and that triple therapy represents the best treatment option available currently. However, the vast majority of those living with HIV/AIDS are unable to access these treatments which are extremely expensive, difficult to adhere to, and require efficiently functioning health and social services.

The consultation recognized 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. Two distinct approaches to providing ARVs emerged during the consultation. One requires that ARVs be provided only when appropriate health and social support systems are in place, while the other supports the provision of ARVs in order to "force" health systems to follow with adequate services.

The consultation reached consensus on a number of 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 industrialized 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 recognized that triple ARV therapy 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 recognized. The assessment of whether the treatment can be properly adhered to, and the decision to start or to continue treatment should be made jointly by the clinician and the patient. Adherence needs to
be nurtured and supported, without violating confidentiality, through a team approach involving nurse, physician, social worker and family.

- 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 and in addition, responsibility for issues such as price regulation, customs and other taxes, quality control, and the monitoring of safety and resistance.

- 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 research on clinical outcomes is essential as none of the currently available ARVs are ideal and a number of promising drugs are under development. In addition, treatment standards and recommendations need to be updated regularly to take into account new data on outcomes and newly registered products.

- The pharmaceutical industry is a key partner in health care, and has social responsibilities as do all civil organizational and institutional bodies. Their collaboration is essential. Continued negotiations involving industry, UN agencies, donors and governments on bulk and preferential prices, on innovative mechanisms, good manufacturing practices, and research priorities is crucial for promoting access to effective ARV therapy.

- 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.

The consultation reached agreement on a number of 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 limited centres of excellence where clinical, laboratory and social support can be guaranteed. Allocating different therapies to subsets of people with HIV-related conditions, taking into account the realities of different settings, may represent a rational strategy offering affordable starting points: prevention of mother-child transmission, post exposure prophylaxis for health workers, treatment of AIDS patients, symptomatic HIV-infected patients and finally asymptomatic HIV-infected patients. Consensus-oriented meetings involving all stakeholders at country level could examine these types of allocations for various settings.

- Because of the high daily turnover of virus production, resistant strains develop very easily. Strict adherence to the drug regimen is therefore essential. ARV combination therapies are not as yet “user friendly” and in conditions of limited support, this frequently leads to intermittent and irregular use. Emergence of resistance should be carefully monitored through a network of collaborating laboratories. WHO/UNAIDS could establish such a coordination mechanism.

- In order to minimize 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 prevention, diagnosis and treatment of opportunistic infections remains an essential component of the clinical management of HIV/AIDS patients. Following WHO’s criteria for
selection of essential drugs, governments need to consider adding drugs for opportunistic infections, other HIV-related conditions and pain management to 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 studies 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. Most RNA assays have been optimized using HIV-1 subtype B, found in industrialized countries. The tests need to be improved to allow accurate detection of the HIV variants most prevalent in Africa, Latin America and Asia. The standardization 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 settings.

- 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.

Given the broad scope of discussions and the divergent views expressed, it was agreed that many questions/issues could not be answered in the context of this consultation. Remaining questions/issues were:

- Do the currently available ARVs justify substantial commitment of public funds? Would it be more rational at this time to wait for the development of drugs for the treatment of HIV infection which are cheaper and easier to take?

- What is the comparative efficacy of different antiretroviral regimens in terms of extending survival and improving the quality of life for people living with HIV/AIDS?

- Is viral load measurement a requirement for triple and double therapy in both asymptomatic and symptomatic patients?

- Should ARVs be included in Essential Drugs Lists?

- Should monotherapy be considered obsolete for treatment of HIV/AIDS and recommended only for reduction of mother-to-child transmission? If it is the only drug available to PLHA, should treatment be withheld?

- If reduced infectivity with new ARV treatments were conclusively demonstrated, might the consensus on voluntary consent for testing and treatment be weakened? Might there be a call for mandatory testing to identify and treat HIV-infected people in order to prevent transmission?
As regards equity of access, much attention has been paid to the issue of distributive justice once the price has been fixed, but little attention has been paid to the ethics of pricing itself. Are current market prices fair or just?

ARV treatments are fraught with difficulties many of which are only starting to be identified and assessed - let alone resolved.

Quality of life has to be carefully considered. Prolonging life and reducing opportunistic infections are measurable improvements. Unpleasant side effects, a very complicated regimen, and the sheer stress of attempting to adhere to this and simultaneously live a fuller life, are just some of the factors which together affect quality of life. Added to this, in some poor settings, is the weight of responsibility of devoting all personal resources and those of the extended family, to these medications. For patients who are asymptomatic, the adverse effects and disruptions to daily life associated with ARVs may actually introduce the first unpleasant effects of HIV infection into their lives.

The development of resistance is always “just around the corner”. It has been shown that minor lapses in adherence may lead to the development of resistance and thus interfere with efficacy. The question has to be posed whether avoiding the risk of transmission of resistant strains is not more important in the long term than allowing patients known to have difficulties in adherence to start or continue therapy.

It is almost certain that given a treatment which is perceived as life saving, but that is prohibitively expensive and hard to obtain, a black market will form; counterfeit drugs will start to circulate and a parallel drug supply system will operate. In this situation, everyone loses out. Patients may buy ineffective products; whilst those receiving quality drugs may use them without medical supervision, increasing the likelihood that resistant strains will develop and spread.

In terms of minimum requirements for the safe and effective use of ARVs, the consultation agreed on the following:

- Availability of reliable, inexpensive tests to diagnose HIV infection and access to voluntary and confidential counselling and testing.
- Adequate management of opportunistic infections including availability of affordable drugs for their treatment and prophylaxis.
- Laboratory facilities with the capacity to run liver function tests, blood count and electrolytes, to monitor for adverse reactions.
- 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, district hospitals to referral centres, with flexible and timely referral and coordination 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 for palliative care and opportunistic infections at the health centre level.
• Joint decision making between physician and patient on all aspects of ARV treatment, including the decision to begin ARVs.

This consultation is the beginning of a process of broadening access to ARVs and any future promising treatments for HIV/AIDS, for all who need them. The process must advance stepwise in conjunction with new discoveries in basic science, clinical and operational research in different settings, the needs and legitimate demands of PLHA, improvements in health and social support services, and evolving government priorities.

The next steps, for WHO in collaboration with UNAIDS in follow up to the consultation will be:

• In response to urgent government requests, technical and policy guidelines on specific issues to be prepared and regularly updated.

• Follow-up technical meetings which will aim to reach consensus on selected key issues.

• A meeting with representatives of the pharmaceutical industry to develop strategies to improve access to HIV-related drugs in low and middle income countries was organized by UNAIDS in June.

• A meeting to review the joint UN strategy on access to drugs for HIV/AIDS and related illnesses based on the collective experiences of WHO, UNICEF, UNDP, UNESCO and the World Bank was called by UNAIDS at the end of June.

All who participated in this consultation explored difficult issues in depth, widened horizons - and learned much in the process. WHO and UNAIDS count on all participants to carry on this reflection in their daily work and to feed back to us and to all the people with whom they work, their insights and eventual conclusions. As one of our participants, a person living with HIV/AIDS said, as she closed the consultation, “This is not an overnight process. Let us build slowly. Each day and each month, more people will have access to ARVs. Let us take it a step at a time, a day at a time - the way I live my life”.

24
The Implications of Antiretroviral Treatments
Informal Consultation
April 1997

Background papers
Treatment of HIV infection:  
Current Recommendations for the Use of Antiretroviral Drugs

Patrick Yeni*

The treatment of HIV infection is rapidly evolving in the industrialized countries. The number of antiretroviral drugs available has increased considerably over the past two years, and the precise requirements for their safe and effective use have been developed, thanks to various recent advances in understanding the pathology of HIV infection, and the development and wider availability of effective tools to measure viral load and disease stage, and thanks to new data from clinical trials. These advances have already led to substantial improvements in the overall health status of HIV-infected people. However, current treatments are associated with certain risks and limitations, which are not insignificant, and their long term effectiveness is not yet known. Further research therefore is needed and current recommendations must be regarded as trends which will continue to evolve.

Currently available antiretroviral drugs and new antiretroviral drugs under development

The number of drugs available for the treatment of HIV infection is increasing rapidly. In 1995 only three (AZT, ddI and ddC) were authorized for use in France. Today, eight drugs are registered (AZT, ddL, ddC, d4T, 3TC, indinavir, ritonavir and saquinavir). Bearing in mind ongoing developments, it is likely that the number of antiretrovirals will continue to increase. In the short and medium term, the new drugs are likely to be of the type that has already been developed (nucleoside analogues and protease inhibitors), but they will have particular characteristics: more intense activity (1529 U89) or activity against strains that have become resistant to other drugs of the same type (ABT-378). A new family of drugs (non-nucleoside inhibitors of reverse transcriptase) are being developed. One of them (nevirapine) is already registered in the USA. The role of antiretrovirals with a totally different mode of action (anti-integrase etc.) is difficult to predict, as is the possible role of immunomodulators (IL2, etc.).

The importance of measuring viral load and CD4 lymphocytes

Studies of cohorts of patients over long periods, both clinically and biologically, have demonstrated the value of measuring viral load and numbers of CD4 lymphocytes for predicting clinical progress. It has been shown that the quantity of HIV RNA in plasma (expressed as number of copies/ml) and the number of circulating CD4 lymphocytes (expressed in mm3) are the two most important parameters to consider. Both are needed as their predictive values are independent. These measures are also important in non-treated patients, because changes in viral load and CD4 count under treatment, assessed in the short term, allow prediction of clinical progress in the longer term, and therefore, therapeutic benefit.

Recommendations have been published on requirements for assessment of viral load. This should be undertaken every six months in non-treated patients, for whom a treatment decision is not required immediately, and every four to six months in patients under treatment. Taking into account the variability of techniques, only a decrease in viral load greater than 66% under treatment indicates significant antiretroviral activity. Defining success and failure of treatment, as measured by changes in viral load, is extremely difficult and the recommendations relating to this are continually evolving. The tendency today is to consider as success a decrease in viral load to undetectable levels, and as failure, any significant increase in viral load above the level achieved under treatment.

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Recommendations for the use of drugs, available in 1997, to treat HIV infection

These are continually updated to take into account availability of new drugs and recent data relating to disease pathology and from clinical trials.

Initial treatment

Taking into account the speed of viral replication and the genetic variability of HIV (the simultaneous occurrence of these two characteristics leads to rapid development of resistant strains), many experts recommend today starting treatment in all patients with a viral load greater than 5000-10,000 copies/ml. The treatment of choice is a combination of two nucleoside analogues and a protease inhibitor. This combination can reduce viral load to undetectable levels in many patients. Practice is evolving towards earlier initiation of treatment with a greater number of drugs in combination. There is as yet no proof that this initial triple therapy can be reduced once the desired effect is obtained, and it is too early to determine the optimal duration of treatment. The possibility of starting treatment with bitherapy of two nucleoside analogues only, reserving the use of a protease inhibitor for later, is being discussed, in particular for patients who are started on treatment when their viral load is not very high. It is not yet known whether this treatment option, which aims to reserve a drug for later but which is less effective than triple therapy, represents an acceptable alternative to triple therapy initiated at the start.

Changing treatment

In the case of intolerance or viral failure, treatment should be changed. When intolerance occurs, as it does frequently, only the drug which is responsible should be changed, if it can be identified. Treatment failure is usually assessed through viral load rather than clinical progress or CD4 count. Incomplete antiviral effectiveness or serious adverse effects should lead to a change in treatment and in particular the prescription of a (new) protease inhibitor. This should be combined whenever possible with at least one other new drug in order to limit the risk of resistance to the protease inhibitor developing - a risk that is very high in monotherapy. Cross resistance to different protease inhibitors makes the choice of an alternative treatment difficult.

Treatment in clinical practice

During 1995, treatment recommendations changed from mono- to bitherapy. In 1996 protease inhibitors became available and their use was recommended in triple therapy (two nucleoside analogues and one protease inhibitor). In the second half of 1996, for the first time in the history of AIDS, a significant decrease (around 21% compared to 1995) in the number of new AIDS cases was observed. Likewise, the number of deaths from AIDS in 1996 decreased by 25% over 1995. Other studies showed a decrease in the days of hospitalization and consultations for HIV infection during this period. The same trends have been reported from other countries, in particular, the USA and Canada. Estimates suggest that cost savings made possible by the greater effectiveness of current treatments could compensate for direct treatment costs.

Limitations of current treatments

Even leaving aside the issue of cost, currently recommended treatments are far from ideal. Secondary effects, observed with most of the drugs in use, are frequent, sometimes serious and they limit treatment effectiveness because one or other of the drugs has to be stopped. Furthermore, nothing is yet known about the long term secondary effects of the most recently developed drugs (particularly the protease inhibitors). Also, current regimens are difficult for several reasons: there is a large number of pills to be taken daily; many of these must not be taken together; their absorption requirements are different making timing of meals difficult - some must be taken with meals, some while fasting; there are strict conditions for keeping the drugs; minor problems,
especially digestive, are very common; there are possible interactions with other treatments (for example, anti-TB). At the same time, dosage requirements to ensure maximum effect and to avoid the development of resistance are very strict.

**Treatment in particular situations**

*Primary HIV infection*

When primary infection has been diagnosed, whether on the basis of clinical or biological markers, intensive treatment should be started (tritherapy with two nucleoside analogues and one protease inhibitor). It is likely that such treatment is more effective in recently infected patients. The optimal duration of treatment is not known.

*Accidental exposure to contaminated blood*

Around 150 cases of HIV infection presumed to have been transmitted through health procedures have been reported amongst health personnel. There are a number of different measures to prevent infection through such accidents. When an accident occurs, post-exposure prophylaxis may be considered. The decision should be based on an assessment of the risk of infection, above all the severity of the exposure and the infectiousness of the body fluid concerned. A case-controlled study reported in 1995 showed that AZT could reduce the risk of HIV infection with contaminated blood by 79% after percutaneous exposure of health personnel. In the case of risk of contamination, preventive treatment should be a combination of AZT and 3TC, to which indinavir (a protease inhibitor) should be added in the case of high risk. The choice of drugs can be modified according to the type and duration of treatment received by the source patient, in order to avoid any resistance to one or more of the recommended drugs that may have developed. The prophylactic treatment should ideally be initiated within four hours of the accidental exposure and should be continued for four weeks.

*Maternal-fetal transmission*

Under specific conditions of maternal immune deficiency and drug administration, AZT has been shown to decrease the baseline rate of perinatal infection by two-thirds (22.6% and 7.6% respectively). It is likely, but not proven, that all pregnant woman irrespective of their CD4 count could benefit from AZT treatment. It is not known however whether AZT retains its effectiveness when it is administered under conditions that stray far from the prescribed regimen: pre and intrapartum treatment of the mother followed by treatment of the newborn for six weeks without breastfeeding. The search for alternative treatments must continue, in particular for women at an advanced stage of infection, or when resistance to AZT is likely, such as for women treated with AZT prior to their pregnancy. However, little data is available on the risks associated with providing other antiretrovirals during pregnancy. It is therefore difficult to establish precise recommendations for non-AZT antiretroviral treatments.
References


Adherence to Antiretroviral Therapy

Graeme Stewart*

Adherence to prescribed medication is often neglected when examining factors contributing to treatment success. However, there is considerable literature on the subject which indicates an average adherence rate for many diseases as low as 50% and a wide gap between the physician's belief and the true level of strict adherence to prescribed drugs (1). Few studies have been published on HIV disease (2-7); their results show equally poor adherence and there are no intuitive reasons to expect otherwise.

However, adherence is particularly critical in relation to ARV treatments. With the recent advent of highly effective combination therapy, survival depends on the prevention of drug resistance; for the most potent agents, there is evidence of resistance resulting from minor lapses in adherence. Optimal antiretroviral therapy has the potential to reduce transmission of disease (from mother to child or by sexual contact or inoculation) by marked and sustained reduction in viral load.

Combination therapy is very expensive; poor adherence means a waste of valuable resources. On the other hand, there is growing evidence that effective, sustained antiretroviral treatment can be cost effective in some settings through the reduction in hospital admissions for opportunistic infections and other HIV disease manifestations (8). The importance of strict adherence to complicated therapy (where affordable and appropriate) has never been greater.

Definition and measurement of adherence

In most studies, adherence is defined as the taking of 80% or more of prescribed therapy. It is commonly measured subjectively by patients reporting to their physician. This can be supported by examination of pharmacy records. AZT consumption can be assessed by showing macrocytosis (MCV>100) as a rough guide. In a clinical trial setting, drug concentrations can be measured and modelled (9). Where available, drop in viral load (CD4 cell count) indicates a drug effect but does not allow quantification of adherence.

Data on antiretroviral adherence

Each of the fully published studies to date preceded the use of protease inhibitors and triple therapy. The higher rate of side effects of current combination therapy suggests that adherence rates will be lower than for AZT unless special efforts are made to address this problem.

In three studies of AZT monotherapy (2,3,4), adherence rates between 67% and 88% were reported in clinical trial settings involving subjective measurement only. Factors associated with adherence were not assessed in these studies. In two more recent studies (4,5), analysing reasons for non-adherence, rates of 42% and 63% were seen for AZT monotherapy assessed by computerized pharmacy records and MCV. One study had limited data on AZT and ddI combination therapy and ddI monotherapy.

Experience has shown that outside the clinical trial setting, adherence is even lower and diminishes over time. In one study, adherence with AZT monotherapy was only 26% at 6 months and declined further on follow-up (10).

* Graeme Stewart, Professor, Westmead Hospital, Australia
Factors influencing adherence to antiretroviral therapy

The factors identified in the HIV literature are listed in Table 1 and are mostly self evident. Knowledge of these should be used to determine the approach to antiretroviral therapy in each patient group and in various clinical settings. In situations where this knowledge would predict a poor level of adherence, the use of triple combination therapy involving a protease inhibitor is difficult to justify. Antiretroviral treatment should be seen in the context of a continuum of care for the HIV infected patient, without which there is no role for these expensive, potentially toxic drugs. (See *The continuum of care: lessons from developing countries* by Dr Eric van Praag in International AIDS Society Newsletter No 3, November 1995.)

Alternatively, there are circumstances where this knowledge can be used to optimise adherence with prescribed combination therapy. Current experience is that ritonavir is not well tolerated and requires forewarning and careful patient selection. Most patients tolerate saquinavir and indinavir well. Lower dose ritonavir given with saquinavir (see Table 4) is better tolerated.

Reasons for failing to receive antiretroviral therapy

Non-adherence should be seen in the broader global context of the many reasons for failure to secure the benefits of the current, potent antiretroviral combinations. These factors are listed in Table 2.

When to start antiretroviral therapy?

Treatment requires knowledge of HIV infection. Starting therapy on the basis of CD4 cell count or viral load in asymptomatic patients (Table 3) requires early detection of HIV. For the large majority of patients worldwide, HIV infection is detected at the first AIDS-defining illness. Early diagnosis of HIV cannot be assumed even in countries in which access to the drugs is well supported. In a study from the UK, 49% of 3556 patients with AIDS became aware of their HIV infection less than 9 months and 37%, less than 3 months before developing AIDS. Those least likely to be aware included heterosexual men and women, younger and older patients and those outside the Thames region (11). In this setting, antiretroviral therapy should be started as soon as possible and will need to take into account interactions with drugs used for opportunistic and other infections such as malaria and tuberculosis.

For patients with early detection of HIV, the current guidelines (Table 3) are not based on trial data and hence the benefit of treatment before the development of clinical symptoms has not yet been proven. The availability of many agents and combinations, and knowledge of the immunopathogenesis of HIV disease underpins the guidelines. The situation is even less clear if only one triple combination regimen is accessible (currently so in several countries).

The problems associated with non-adherence make most HIV physicians very reluctant to start triple therapy without a strong commitment from their patient and a support network to optimize strict adherence. The treatment of primary HIV infection (when recognized) represents a special case. Due to the potential for improving prognosis and the theoretical possibility of eradication of infection, many physicians recommend immediate triple therapy (12). Again, this is in patients likely to comply as the rapid viral turnover makes the emergence of resistance even more of an issue.

The addition of viral load to the treatment guidelines may substantially increase the number of eligible patients: in a recent study of patients with a CD4 count over 500, one quarter had a viral load greater than 30,000 and one half, greater than 10,000 copies/ml (13).
Laboratory support for treatment decisions

It is difficult to manage combination therapy without plasma HIV RNA (viral load) measurement. A drop in viral load (at least 0.5 log10 or threefold) at one month indicates efficacy (although the goal is to achieve undetectable levels whenever possible) and a degree of adherence. Viral load measurement is valuable in reinforcing the benefit of treatment and the importance of further adherence despite side effects and inconvenience. The rise in CD4 cell count which usually accompanies the drop in viral load reinforces this message particularly in patients who have followed their CD4 count for years. Conversely there is no point in continuing a regimen that is not reducing viral load. Plasma HIV RNA measurement should then be monitored at least 3 to 4 times per year (more often when it starts to rise again). Whilst the test is expensive (about US$ 200 per assay) several viral load tests cost the same as one month's combination therapy (see Table 2) - treatment that may be wasted. If the regimen is tolerated and a clinical response seen, it is usually continued until the viral load returns to pre-treatment level. (Physicians vary on this issue.) CD4 cell measurement continues to have benefit mostly in decisions on prophylaxis and prediction of opportunistic infection.

Monitoring side effects

Apart from regular clinical assessment (preferably monthly), access to laboratory measurement of full blood count, liver function and amylase (for drugs associated with pancreatitis) is vital. In patients with coexisting hepatitis B infection, the improvement in immune function that may follow treatment with protease inhibitors may result in a flare up of hepatitis.

Who should prescribe combination antiretroviral therapy?

Medical management of the HIV infected patient must involve shared care between primary care physicians (GP) and specialists, with the GP carrying out those tasks with which he or she is comfortable. With the current array of drugs and uncertainty over their best use, specialist knowledge and experience are necessary for decisions about starting and changing ARV therapy. Monitoring for efficacy and toxicity can be done by the GP. In parts of Australia, GPs with high HIV caseloads can receive prescribing rights following completion of a training course; it remains an unresolved area of contention for some. The Australian Society for HIV Medicine (ASHM) with membership available to both GP and specialist provides an important forum for the ongoing resolution of issues in clinical practice and runs training and continuing education programmes. ASHM has produced two books for Australian doctors with government funding, "Could it be HIV?" (1994) and "Managing HIV" (1997). It works closely with affected communities and perhaps provides a model for other countries.

Drug interactions

Multiple pharmacodynamic and pharmacokinetic interactions occur between the antiretroviral agents and the many drugs used in HIV medicine. Some are of particular importance to countries with a high prevalence of TB. Important examples include:

- **ddI**: reduced bioavailability (due to buffer) of fluoroquinolones (ciprofloxacin, norfloxacin) dapsone, isoniazid, itraconazole, ketoconazole, tetracyclines (eg doxycycline), delavirdine. Can be decreased by separate administration (1 hour or more).
- **indinavir**: increased serum concentration of rifabutin, rifampin; increased risk of cardiac toxicity with cisapride, terfenadine, astemizole.
- **ritonavir**: increased serum concentration of alprazolam, clarithromycin, diazepam, erythromycin, ketoconazole, itraconazole, rifabutin, saquinavir, tricyclic antidepressants (eg desipramine); loss of efficacy of oral contraceptives.
Treatment of concurrent HIV and TB

Prompt and effective treatment for TB in the HIV-infected patient is critical to clinical response and the prevention of transmission to others. Rifampin is an essential component of the recommended regimen for TB. The protease inhibitors increase the serum levels of the rifabutins (rifampin and rifabutin) and thus increase the risk for toxicity. Rifampicins, through the induction of hepatic cytochrome p450, increase the metabolism of protease inhibitors and thus decrease serum concentrations - often to subtherapeutic levels. Guidelines from the US Public Health Service have been recently published (13). The importance of prophylaxis with isoniazid for all HIV infected patients at risk for TB should be stressed. For those coinfected, the dosage needs to be tailored to the situation. If therapy with protease inhibitors is being considered it is advised to complete TB treatment first. For patients already taking a protease inhibitor, there are three options:

1. Discontinue treatment with protease inhibitor and initiate short course (minimum 6 months) anti-TB regimen containing rifampin.

2. Discontinue treatment with protease inhibitor and initiate 2 month, 4 drug anti-TB regimen containing rifampin. Following bacteriological response and drug tests confirming susceptibility to INH and ethambutol (approx 3 months), decrease anti-TB regimen to 2 drugs and reintroduce protease inhibitor.

3. Continue protease inhibitor (indinavir) and initiate a 4 drug, 9 month TB treatment regime containing daily rifabutin. Patients require careful monitoring, possibly including serum levels (available only in specialized laboratories).

Options 2 and 3 require extended TB treatment, repeated bacteriological evaluation (during and after treatment), directly observed treatment and careful monitoring for drug toxicity. In the future data may show that concurrent use with dosage adjustment to compensate for drug interaction may be possible.

Dosing schedules

Taking combination therapy can be complicated due to i) the need to take drugs such as ddI separately, ii) the need to take certain drugs with meals and others while fasting, iii) the advisability of 8 hourly dosing with indinavir and, iv) interactions with other drugs. Instructions to patients are provided in Table 4. They require understanding, organization and commitment. Support from the pharmacist is essential (drug card, interview etc). Typical daily drug regimens are shown in Table 6.

Minimum requirements for prescribing combination antiretroviral therapy

From the above considerations it appears important for HIV physicians to consider the minimum requirements in their practice setting (and/or with each individual patient) to ensure the level of adherence needed to justify the potential toxicity and future loss of efficacy, inconvenience and cost of combination therapy. Commitment is likely to be greater in patients who are symptomatic (or have recovered from an opportunistic infection), than in those who are asymptomatic (Table 3). In the latter case, particular attention needs to be paid to the factors influencing beliefs about health (Table 1). On the other hand, patients with advanced HIV disease are more likely to be taking many other medications, to suffer more side effects and to have reduced independence. In all cases, homelessness, current IV drug use, lack of understanding, commitment, and social support, depression and poor doctor patient rapport, are factors contributing to poor adherence. It is difficult to determine minimum requirements for adherence to cover all countries and practice settings; guidelines have been attempted in Table 5.
<table>
<thead>
<tr>
<th>Table 1: Factors influencing adherence to antiretroviral therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Drug Regimen</td>
</tr>
<tr>
<td>• toxicity</td>
</tr>
<tr>
<td>• number of medications</td>
</tr>
<tr>
<td>• dosage frequency</td>
</tr>
<tr>
<td>• inconvenience (lifestyle change)</td>
</tr>
<tr>
<td>• need to ritualise or integrate drug taking</td>
</tr>
<tr>
<td>• duration of treatment into daily routine</td>
</tr>
<tr>
<td>2. Social Support</td>
</tr>
<tr>
<td>• home</td>
</tr>
<tr>
<td>• people (partner, family, friends, NGO)</td>
</tr>
<tr>
<td>• facilities</td>
</tr>
<tr>
<td>• cost of drugs</td>
</tr>
<tr>
<td>• ease of access to clinic</td>
</tr>
<tr>
<td>• level of independence</td>
</tr>
<tr>
<td>3. Health Benefits/Education</td>
</tr>
<tr>
<td>• perceived risk</td>
</tr>
<tr>
<td>• perceived benefit - previous opportunistic infection</td>
</tr>
<tr>
<td>• conflicting opinions (doctor, media, community)</td>
</tr>
<tr>
<td>• socio - cultural concepts of illness</td>
</tr>
<tr>
<td>• community based education</td>
</tr>
<tr>
<td>4. Psychological Factors</td>
</tr>
<tr>
<td>• depression (self-neglect, apathy, forgetfulness)</td>
</tr>
<tr>
<td>• poor adaptive coping</td>
</tr>
<tr>
<td>• anxiety</td>
</tr>
<tr>
<td>• IV drug dependence</td>
</tr>
<tr>
<td>5. Doctor-Patient Interaction</td>
</tr>
<tr>
<td>• continuity</td>
</tr>
<tr>
<td>• communication (verbal, non-verbal)</td>
</tr>
<tr>
<td>• perceived prejudice</td>
</tr>
<tr>
<td>• disparity in race, social class, ethnicity</td>
</tr>
<tr>
<td>• team approach (counsellor, NGO, etc)</td>
</tr>
<tr>
<td>• trust</td>
</tr>
<tr>
<td>• ease of access to medical care</td>
</tr>
</tbody>
</table>

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Table 2: Reasons for failing to receive antiretroviral therapy

1. **HIV infection not diagnosed**
   - need for test known
   - need not known

2. **Lack of specialist medical care**
   - not available
   - not accessible
   - failure to attend

3. **Variation in physician practise**
   - lack of agreed guidelines
   - unavailability of critical tests
   - (CD4 cells, viral load)

4. **Drugs not available**
   - not approved
   - not affordable
   - unreliable supply

5. **Initial prescription refused**
   - benefit not agreed
   - fear of toxicity
   - non-adherences factors

6. **Non-adherence with therapy**
   - (see Table 1)
Table 3: Recommendations for when to initiate treatment

Symptomatic HIV disease*
Therapy recommended for all patients

Asymptomatic

CD4 cell count <500/μL: Therapy recommended+
CD4 cell count <500/μL: Therapy recommended for patients with > 30 000 - 50 000 HIV RNA copies/mL or rapidly declining CD4 cell counts. Consider therapy for patients > 5000 - 10 000 HIV RNA copies/mL.

* Symptomatic HIV disease includes symptoms such as recurrent mucosal candidiasis; oral hairy leukoplakia; chronic or otherwise unexplained fatigue; night sweats or weight loss.

+ Some would defer therapy in a subset of patients with stable CD4 cell count between 350 and 500/μL and plasma HIV RNA consistently below 5000 - 10 000 copies/mL.
Table 4: Dosage regimen and cost of antiretroviral drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dosage</th>
<th>Instruction</th>
<th>Cost US$/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>250mgs bd</td>
<td></td>
<td>3340</td>
</tr>
<tr>
<td>*ddl</td>
<td>200mgs bd</td>
<td>empty stomach</td>
<td>2300</td>
</tr>
<tr>
<td>3TC</td>
<td>150mgs bd</td>
<td>empty stomach</td>
<td>2690</td>
</tr>
<tr>
<td>ddC</td>
<td>0.75mgs bd</td>
<td></td>
<td>2486</td>
</tr>
<tr>
<td>d4T</td>
<td>40mgs bd</td>
<td></td>
<td>2900</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nevirapine</td>
<td>200mgs tds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*delavirdine</td>
<td>400mgs tds</td>
<td>empty stomach</td>
<td></td>
</tr>
<tr>
<td>Protease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>saquinavir</td>
<td>600mgs tds</td>
<td>within 2 hours of a meal</td>
<td>6870</td>
</tr>
<tr>
<td>*indinavir</td>
<td>800mgs tds</td>
<td>empty stomach</td>
<td>4320</td>
</tr>
<tr>
<td>ritonavir</td>
<td>600mgs bd</td>
<td>with meals, refrigerate</td>
<td>8010</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>750mgs tds</td>
<td>with meals</td>
<td></td>
</tr>
</tbody>
</table>

*space 2 hours apart
NB: saquinavir 400 mgs bd can be given in combination with ritonavir 400 mgs bd
Table 5 : Minimum requirements for prescribing combination antiretroviral therapy

1. Drug regimen
   - acceptable side effects
   - achievable routine/lifestyle change
   - routine fully understood
     * drug card with full instructions
     * discussed with pharmacist
   - agreed plan if unable to adhere to treatment
   - all potential drug interactions known by physician
   - possibility of concomitant TB treatment considered

2. Social support
   - affordable drugs
   - adequate housing
   - facilities for storage, dispensing
   - responsible other, if not independent
   - assured transport etc for clinic visits

3. Health beliefs/education
   - full understanding of benefits of treatment
     * discussion with physician and others
     * written information
   - knowledge of relevant aspects of HIV disease
   - ongoing access to information/reinforcement

4. Psychological factors
   - Problems associated with dementia, depression, current IV drug use, or other disorders known and addressed

5. Doctor - patient relationship
   - continuity of care planned before prescribing (including “shared care” between specialist and GP)
   - trust
   - easy access to health care team for problems
## Daily Drug Regimen - Patient 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug</th>
<th>Tablets</th>
<th>Comments / Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0600</td>
<td>DDI</td>
<td>2</td>
<td>EMPTY STOMACH</td>
</tr>
<tr>
<td></td>
<td>INDINAVIR</td>
<td>2</td>
<td>NEED TO SET ALARM MAY WANT TO SLEEP</td>
</tr>
<tr>
<td>0700</td>
<td>3TC</td>
<td>1</td>
<td>NEED TO EAT OTHERWISE</td>
</tr>
<tr>
<td></td>
<td>CLARITHROMYCIN</td>
<td>1</td>
<td>STOMACH PAIN/NAUSEA</td>
</tr>
<tr>
<td></td>
<td>ETHAMBUTOL</td>
<td>3</td>
<td>AVOID MILK</td>
</tr>
<tr>
<td></td>
<td>CIPROXIN</td>
<td>1</td>
<td></td>
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**Current Side Effects and Additional Comments:**

NAUSEA - DIARRHOEA
PREFER TO WAKE UP LATER AND GO TO BED EARLIER BUT CANNOT DISTURBS FOOD INTAKE PATTERN
ANXIETY IF MISS DRUG BY MORE THAN 1/2 HOUR OR MORE

40
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CURRENT SIDE EFFECTS AND ADDITIONAL COMMENTS:
References


Resistance to Antiretroviral Drugs

Mark Wainberg

Introduction

HIV-1 viral resistance against antagonists (i.e. antiretroviral drugs) of the viral reverse transcriptase (RT) and protease enzymes is due to a series of mutations in the genes that encode these respective enzymes. Mutations occur due to the error-prone nature of HIV RT itself that is responsible for copying the HIV genome. The error rate of HIV RT is estimated at approximately $10^{-4}$. This means that one mutation in the RT-directed synthesis of viral DNA will occur, on average, once during every virus replication cycle, given a genomic length of 9.2 kb. While many such mutations may be inconsequential or silent, many may also be lethal. In both of these situations, it may be impossible to determine whether mutations have arisen, since in the first case there may be no substitution in amino acid sequence while, in the second, viral replication might not take place.

Accordingly the most effective way to recognize mutagenesis is under conditions of selective pressure, as is exerted during the course of HIV disease by both antiviral drugs and the immune system. In the first case, spontaneously occurring mutations in either the HIV RT or protease genes may be amplified under conditions of drug pressure to yield drug resistant forms. In the case of immunological pressure, HIV variants may emerge that are no longer reactive against neutralizing antibodies and/or cytotoxic T lymphocytes, due to mutations in epitopes that might otherwise have been recognized by these immune effector mechanisms. In this context, the principles that govern the emergence of drug-resistant viruses are similar to those that define bacterial resistance to antibiotics and the resistance of cancer cells to onco-chemotherapeutic regimens.

Of course, HIV mutagenesis is an ongoing process. This means that mutations that encode drug-resistant variants can take place both prior to the administration of antiviral drugs as well as during antiviral therapy, as long as the drugs utilized are unable to completely shut down virus replication. Mutated viruses that are not amplified by conditions of drug pressure may never be recognized, since they may be present only as a tiny fraction of the much larger quasispecies. In addition, mutated viruses in untreated individuals are probably unable to replicate faster than wild-type viruses, since they would otherwise become the dominant population in the absence of antiviral therapy.

HIV Reverse Transcriptase

HIV reverse transcriptase (RT) converts viral genomic RNA into double-stranded proviral DNA. This essential role has made this enzyme a primary target of antiretroviral chemotherapy. RT inhibitors can be classified into two major groups based on structural considerations: nucleoside analogs (NRTI) and non-nucleoside RT inhibitors (NNRTI), that act in different ways to block HIV-1 RT polymerase activity. Nucleoside analogs are 2', 3'-dideoxy derivatives of the natural substrates, i.e., 2'-deoxynucleosides, of DNA polymerases. All 2', 3'-dideoxynucleoside analogs are thought to act in similar fashion to inhibit RT activity (1-2). Following intracellular phosphorylation to 5'-triphosphorylated forms (ddNTT), they competitively interfere with the binding of natural substrates to RT and are incorporated into elongating DNA strands. Chain termination then results from the lack of a hydroxyl group at the 3' carbon of the pentose ring of the nucleoside antagonist, without which a 3'-5' phosphodiester bond cannot be formed with an incoming substrate.

* Mark A. Wainberg, McGill University AIDS Centre, Montréal
NNRTIs are a group of highly specific inhibitors of HIV-1 RT that bind to a hydrophobic pocket near the polymerase catalytic site of RT (3). Although the precise mechanisms of action of NNRTI are unclear, they apparently act as non-competitive inhibitors of RT.

RT inhibitors can decrease the viral load of HIV-1 infected individuals (4). However, patients commonly suffer clinical deterioration, once drug-resistant viruses appear during prolonged therapy (5,6).

In the case of AZT monotherapy, most evidence indicates that HIV drug resistance is probably causally associated with treatment failure and death. However, such findings might be much harder to demonstrate in the case of patients receiving three or more antiviral drugs, due to higher numbers of confounders associated with more complicated regimes.

Drug-resistant viruses were first isolated from individuals treated with 3'-azido- 3'-deoxythymidine (azidohymidine, zidovudine, AZT, ZDV). Although resistance to NNRTIs can develop quickly, resistance to nucleoside analogs usually takes about 6 months in vivo, with the exception, of the (+) enantiomer of 2', 3'-dideoxy-3'-thiacytidine (lamivudine, 3TC) (7).

To date, resistance-conferring mutations in HIV RT have been reported for all nucleoside and NNRTI compounds used to treat patients infected with the virus. Different patterns of drug sensitivity and resistance have emerged, however, even among members of the same drug class. In some cases HIV may remain relatively sensitive even after mutations develop. For example, a 100-fold drop in sensitivity to zidovudine (AZT) may develop after six months of monotherapy, while only several weeks of monotherapy with lamivudine (3TC) may result in high-level resistance to the latter agent. In regard to the three other commonly employed nucleoside analogues, i.e. didanosine (ddI), zalcitabine (ddC), and stavudine (d4T), HIV may remain fairly sensitive even after the appearance of specific resistance-conferring mutations.

The IC50 is the concentration of drug that can inhibit viral replication in culture by 50%. Thus, low IC50s denote susceptibility while high IC50s denote loss of susceptibility or resistance. An increase in IC50 is usually demonstrated over time, concurrent with an increase in the relative proportion of drug-resistant viruses as analyzed by selective polymerase chain reaction (PCR) for detection of mutated sequences in the RT gene. Sometimes, the in vivo development of resistance to nucleoside analogs can occur independently of drug dose. In the case of AZT, less than a 3-fold increase in IC50 is considered to be within the normal range of variation, while a 10-50 fold increase in IC50 denotes partial resistance. IC50 increases above 50-100 fold represent high-level resistance.

HIV drug resistance can also be selected in cell culture by gradually increasing the concentrations of any of the nucleoside analogs, NNRTIs or protease inhibitors. HIV drug resistance commonly appears faster in cell culture under drug pressure than in the clinic. This may be due, in part, to the fact that HIV can replicate faster in transformed cell lines than in healthy T lymphocytes. However, the same resistance-conferring mutations that arise in cell culture are also seen clinically (8). Thus, tissue culture selection provides a fast and efficient way to study HIV-1 drug resistance and identify resistance-conferring mutations, even before the initiation of clinical trials that utilize the same drugs.

Protease inhibitors

Mutations leading to resistance to protease inhibitors (PI) are concentrated in the substrate binding pocket of the protease enzyme. Since protease inhibitors act by binding directly to the active site of the viral enzyme, it was predictable that mutations arising at amino acids at the binding site would affect binding. At least 40 mutations in the HIV protease enzyme have now been identified that confer some degree of resistance against each of saquinavir, ritonavir, indinavir, and nelﬁnavir (9). These are the
principal compounds used to date to antagonize the HIV protease enzyme. Each of these drugs continues to be studied in clinical trials, and approval for all of them has been granted by the Food and Drug Administration (FDA) of the United States.

Other considerations

Other considerations in regard to resistance include the concept of "genetic barrier". One reason that high-level resistance to AZT takes long periods, i.e. 6 months to 2 years, to develop, may be the number of mutations that must be present and selected for under drug therapy. The same is true in regard to certain protease inhibitors, e.g. indinavir. In contrast, resistance might be expected to develop much more rapidly in the case of resistance conferred by single substitutions, e.g. M184V and 3TC. In some cases, plasma drug levels are important and may be higher than the susceptibility levels of any resistant viruses that are present.

An additional consideration is that drug-resistant viruses may be responsible for some cases of primary HIV infection (10). Presumably, both sexual transmission of drug-resistant variants as well as transmission of such viruses by users of intravenous drugs may both occur. The extent to which such viruses may be involved in cases of primary infection may be expected to increase, in view of the high percentage of viral isolates that display resistance to various anti-viral drugs. It is also apparent that issues of adherence in regard to therapeutic regimens are rapidly becoming important, since incomplete suppression of viral replication, i.e. sub-optimal anti-viral pressure, may be expected to lead to drug resistance in virtually all cases. This subject is of obvious importance in regard to public health.

Another important issue is that of preventing vertical transmission of HIV from pregnant women to their offspring. AZT has been shown to significantly diminish such transmission, raising the question of whether such treatment should be initiated in resource poor countries. The answer to this question is "yes", on condition that treatment be discontinued immediately after delivery. This will help prevent vertical transmission and avoid the emergence of AZT-resistant strains, which would be likely if AZT monotherapy were continued over a protracted period. Moreover, no clinical benefit for the woman would be expected in the context of AZT monotherapy treatment. At the same time, the proposed regimen should preserve the benefit of AZT in the prevention of vertical transmission during future pregnancies.

To overcome or prevent resistance, it will probably be necessary to suppress viral replication. As an example, resistance mutations were less likely to be present in patients who took AZT plus ddl, and who had sustained reductions in viral load, than in individuals on the same regimens but who had only transient reductions in viral load (10). Of course, resistant viruses cannot outgrow the wild-type population, which is also most fit, in the absence of drug pressure. Antiretroviral therapy will select for outgrowth of mutated viruses and increased selective pressure may, therefore, increase the likelihood that resistance will occur. However, if viral replication is shut down through use of effective combination therapeutic regimens, the possibility of resistance will be reduced, since non-replicating viruses cannot mutate into resistant forms in the first place. More efficient suppression of virus replication is now being achieved through use of combinations of drugs, including nucleosides, NNRTIs and protease inhibitors.

Finally, it should be noted that increased emphasis should be placed on drugs that do not need to be metabolized in order to achieve an antiviral effect. This includes the NNRTI drugs that act directly to block HIV RT activity as well as compounds that can antagonize the function of the viral nucleocapsid (NC) protein. Such drugs might have utility as topical virucidal agents, can be relatively inexpensive to produce, and might be of great importance in developing countries to prevent the spread of HIV. In this context, unlike that of a treatment scenario, drug resistance would not be expected to occur.
References


Laboratory Monitoring for Antiretroviral Treatments

Professor Lutz Gurtler*

HIV pathogenicity

HIV’s pathogenic action, which leads to immunodeficiency, occurs in two ways: by virus replication and by progressive destruction of the immune system. The pathogenic action results from the virus’s toxic capacity to destroy cells, to interfere with cell communication and to paralyze cell action. Induction of apoptosis is another way in which the number of competent immune cells are reduced. Viral replication takes place at a rate of up to 100 million particles per day. Replication is dependent on the structure of the virus, i.e. the nucleic acid sequence of ltr, tat, rev and nef genes and therefore, the activity of viral activation factors. Additionally, viral replication is dependent on the cellular activation factors of the host, such as NF-κB, that accelerate and sustain the replication cycle. Products from opportunistic agents like cytomegalovirus, hepatitis virus C and bacteria may also accelerate HIV growth.

The waning immune function leads to inefficient clearance of viral particles, adsorption and neutralization of viral components and destruction of cells expressing viral structures on their surface. The immune system copes for some time, allowing the patient to survive on average for 8 to 10 years, and then collapses. Long term non-progressors may survive for more than 14 years without destruction of their immune function. The capacity of the immune system to combat HIV efficiently is age dependent - people older than 35 years have an “aged” immune system and decreased capacity.

Antiretroviral therapy is most effective when the immune function is still good. A damaged immune system under antiretroviral therapy will be partially reconstituted but not restored. Viral replication rate and viral clearance by the immune system have to be considered together.

Inhibition of retroviral enzymes

The high mutation rate of HIV (1 mutation per cycle of replication) results in continual changes in the envelope structure and thus to the generation of escape variants which are resistant to the drugs. Drugs can potentely interfere with the function of enzymes. The more they stick to the pocket of the active centre of the enzymes, and the stronger the binding is, the more mutations will be needed to inhibit their action. Some viruses however, have been shown to be naturally resistant to certain drugs: one example is nevirapine and its failure to inhibit the replication of HIV-2 and HIV-O.

During the HIV life cycle three enzymes may be inhibited: the reverse transcriptase (RT), the protease (PR) and the integrase (IN). Several drugs which inhibit RT by different modes of action have been used singly and in combination for some time. For PR inhibition, three drugs are currently available, only two of which may be combined. IN inhibitors are still under development. Due to the high mutation rate in the replication cycle of HIV, monotherapy has led to drug resistance within 6 weeks in vitro, although in some patients, it may take more than one year for resistant strains to appear. In theory, efficient RT inhibitors will lead to a 1 log 10 or 90% reduction in viral load. A similar figure is valid for treatment with PR inhibitors. Drug combinations will have an additive effect so that 2 log 10, or 99% reduction in viral load can be achieved.

Final elimination of HIV, which requires the support of the immune system, could only be achieved with a permanent 3 log 10 virus load reduction obtained with drug treatment. This appears

* Lutz Gurtler, Professor, University of Munich
unlikely with combinations of RT and PR inhibitors only. Elimination of HIV might take more than 7 years after the start of treatment, as there are foci of low production and persistence of virus in the brain and lymphoreticular system.

As treatment is usually started in immunocompromised patients, an efficient antiretroviral therapy has to be combined with substances that lead to restoration of the immune function. Commonly used drugs are interleukin-2 and thymosin derivatives.

Laboratory methods to monitor the viral load in patients

To date, three methods to quantify HIV content are available commercially: the polymerase chain reaction by Roche (1), the branched DNA signal amplification assay by Chiron (2), and the isothermic nucleic acid amplification by Organon (3). All procedures can be performed in plasma and serum and, with some modifications, also in whole blood. Reliable results are obtained when the plasma is separated from cellular components within 4 hours of drawing blood. Plasma should be kept at 4°C and if not used within the next 24 hours it should be stored at -70°C or lower. A temperature of -20°C is not sufficient for long term preservation of the specimens and will lead to continuous decay of viral particles.

HIV replication in the central nervous system

Determination of viral load in cerebrospinal fluid (CSF) is the most accurate laboratory method to analyse HIV replication in the central nervous system (7). In consequence drugs that penetrate the CNS have to be used when the CNS is a focus of HIV replication.

Neonates

Qualitative detection of HIV nucleic acid, either by incorporated DNA from cells or RNA from body fluids, is needed to identify infected neonates at birth or in the following months. Delayed growth, and prolonged suffering from childhood and opportunistic infections, will be used as indications of HIV status. The vaccination programme of a child has to be tailored to the infected child’s clinical condition. Thus performance of nucleic based technology without quantification is a priority before any quantitative analysis is undertaken.

p24-antigen test

This is an ELISA test based on the use of different monoclonal antibodies to determine the free inner core protein of HIV in plasma. Free p24-antigen may be shed from infected cells and may be present in high quantities in plasma. However, the virus particles may be undetectable due to complexation with p24 antibody from the patient which will interfere with the assay and lower its sensitivity. Compared to the viral load assay, this assay is insensitive. There is no correlation between viral load and p24-antigen level.

HIV types and subtypes

None of the three 3 nucleic acid amplification procedures can be used to amplify HIV-2 and HIV-0 nucleic acids. They can therefore only be used for monitoring HIV-1 (group M) infection. HIV-1 may be divided into the subtypes A to J (4) of which A to E are the most important. The primers designed for nucleic acid amplification are best suited to amplify HIV-1B which is the virus most prevalent in Europe, North America, South America and Australia. In Asia, subtypes HIV-1B, HIV-1C and HIV-1E are prevalent (5). HIV-1E is different from the HIV-1A only in the env part; HIV-1C
is related to HIV-1A. HIV-1D is the most heterogeneous subtype and is related to some extent to HIV-1B. All HIV-1 subtypes are found in sub-Saharan Africa.

Subtyping of HIV-1 is complicated by the potential of two HIV subtypes to form recombinant viruses (4,5,6). Recombinants of HIV-1 and HIV-O, and of HIV-1 and HIV-2 have not been found. Detection of HIV nucleic acid is dependent on the extent to which sequences are conserved compared to HIV-1B. Through a series of recombination events, part of the nucleic acid of a patient's HIV might originate from HIV-1A, another part from HIV-1B and the last part from HIV-1D. Amplification will depend on the stringency of the primer binding and this means that when an HIV-1B is amplified with an efficiency of 100%, an HIV-1A might only be amplified with an efficiency of 40% or less. The more primers used in the assay or the more that are chosen from highly conserved genome regions, the higher the probability that a correct amplification product will be obtained.

Techniques and equipment

The price per assay (from the three companies) for one specimen is officially US$ 100.

PCR

Extraction of RNA is carried out by column chromatography in small one-way columns. The HIV-RNA is then transcribed to DNA and several rounds of cycles yield the exponential amplification of pieces of DNA in the presence of control-DNA. The fragment size of the pieces is dependent on the primer binding sites. For amplification, a special apparatus - thermocycler - is needed (cost: between US$ 5000- 10,000). The amplified product (amplificate) is hybridized to a probe and quantified by measurement of the microtiter plate in a photometer. The time needed for performing one assay is 8 hours. Sensitivity is 400 copies/ml.

Special procedures, conditions and skills are absolute prerequisites to avoid contamination. At least three rooms are recommended for performing PCR. With the Roche assay, there is a possibility of enzymatic destruction of the amplificates. The Taq polymerase involved in the assay is sensitive to inhibition by several substances like heparin, haemoglobin and drugs.

When PCR is performed in a laboratory, additional assays for the prediction of cofactors of the outcome of HIV infected patients, such as determination of the chemokine receptors or the chemokine expression, can be performed with the same equipment.

b-DNA assay

To increase sensitivity, HIV is concentrated from 1 ml of plasma by ultracentrifugation (cost of apparatus: around US$ 10,000). The viral particles are broken and RNA liberated. The HIV-RNA is subsequently bound to probes fixed on a microtiter plate and simultaneously, a set of primers for the following amplification process are bound. To the primers, nucleic acids are hybridized that carry binding sites to alkaline phosphatase which then converts a chemoluminescent dye. Measurements are made in a chemoluminescinometer for 24 hours (cost: US$ 40,000).

The b-DNA assay does not carry the risk of sample contamination by the amplified product. Sensitivity is around 500 RNA copies /ml, and around 100 in a revised assay. Detection of HIV-1 subtypes with this assay seems to be superior to the PCR assay.
NASBA

Viral RNA is extracted by silicagel binding. After primer attachment and further processing, the RNA is amplified by T7-polymerase. The amplified product is quantified according to standards and after hybridization, to a ruthenium labeled probe on magnetic beads. Light emission of the ruthenium labeled probe that has been purified after hybridization by affinity adsorption, gives the quantitative signal.

Since the amplification process is isothermal at 41°C no special instrument is needed. The apparatus for quantification and purification of the beads costs US$ 40,000. The time needed to perform the assay is 12 to 16 hours. The sensitivity goes down to about 500 copies/ml, and with lower accuracy to 100 copies/ml. The quantification of subtypes is the same as for PCR.

Sensitivity of the assays and daily fluctuation of the viral load in a single patient

It has been claimed that assays with an accurate measurement of HIV-RNA copies down to 20 are needed. It is true that during effective treatment, the number of copies may come down to a level that is no longer measurable, which means 0 copies/ml. Daily fluctuations in viral load may be very large (more than 10 fold) due to intense muscle activity brought on by stress, flourishing superinfections or malnourishment. What is needed therefore is not extreme sensitivity but rather, measurement of the viral quantity over time, which means months and years.

Relationship of viral load to number of CD4 cells

In some patients, during ineffectve treatment, the viral load decreases, associated with a decline in the number of CD4 cells. The reason is the burn out of newly generated CD4 cells, which HIV needs for replication. Determination of viral load without a CD4 cell count might be wrongly interpreted as an indication that the patient's status has improved. In other patients, after starting treatment, CD4 cell count increases and then stabilizes after several weeks to a constant level. It may decline again when the condition worsens, independent of the viral load in plasma. HIV viral load therefore, has to be determined and considered together with the CD4 cell count.

Quantification of CD4 cells

The most accurate and reliable method is FACS analysis (8,9). FACS stands for fluorescent activated cell sorter. The instrument is used in all laboratories providing services for AIDS patients in industrialized countries. It costs between US$ 30,000 and US$ 50,000. As special reagents are required, one analysis can cost up to US$ 40. More tedious and less reliable is the slide microscopy immunofluorescence with antibodies against CD3, CD4 and CD8 labelled with different fluorochromes. This method is a laborious and only rough estimate of the cellular immune status of the patient. The price for a fluorescence microscope is around US$ 20,000 and the price per assay is US$ 2-3. Other methods to determine CD4 counts exist that may be useful to laboratories with limited technical capacity, such as the alkaline phosphatase and Coulter Counter’s bead methods.

Further tests needed to monitor HIV infected and AIDS patients

Antiretroviral drugs have serious side effects including anaemia, leukocytopenia and less frequently thrombocytopenia. When antiretroviral therapy is started, instruments for the quantification of blood cells are an absolute necessity (the price per instrument is US$ 10,000, per analysis US$ 1).

The majority of AIDS patients have recurrent episodes of opportunistic infections. In developing countries tuberculosis is of particular concern. Other infectious agents are
cytomegalovirus, cryptosporidia, candida, cryptococcus, toxoplasmosis and common bacteria. Antiretroviral agents may prevent the occurrence of opportunistic infections. However, when antiretroviral treatment fails or when drugs are no longer taken, there may be an enormous burst of viral activity and opportunistic infections will reappear. Detection of opportunistic agents by either culture or PCR (or both) is therefore desirable and detection by special microscopic examinations is essential. In conclusion laboratory facilities and appropriate instruments for the detection of opportunistic infections have to be available before quantification of HIV load is started.

**Determination of HIV drug resistance**

When patients have already been treated with monotherapy, for example AZT (zidovudine), their HIV strains or quasispecies will develop resistance to drugs more quickly than in untreated patients. Drug failure usually starts in these patients 6 to 12 months after the start of therapy. Several assays have been developed to determine drug resistance.

The biological or phenotypic test measures HIV growth in the presence of different concentrations of the drug or a combination of drugs. The performance of the assay is dependent on a P3 facility and the isolated or cloned virus/enzyme. The assay is cumbersome, time consuming and very expensive and thus not recommended for general use.

The genotypic assay determines the mutations within the nucleic acid of the patient's HIV RT or PR genome and when the amino acid exchanges causing resistance are known, the degree of resistance can be calculated. This assay can be performed within 3 days, but needs laboratory capacity for nucleic acid sequencing. The price for the equipment to do sequencing is between US$ 20,000 and US$ 100,000, price per analysis of resistance is US$ 20.

Drug resistance to PR within the available drugs is closely linked. A virus that developed resistance to indinavir is resistant to ritonavir as well and less susceptible to saquinavir. Mutations causing resistance within the RT to ddi will influence ddC as well, while AZT and 3TC might have opposite effects in the mutation, for example of M184V. All relevant mutations can easily be seen when HIV genome sequencing is performed.

Ongoing drug resistance can be monitored independently of the HIV enzyme gene sequencing by observing increasing HIV load and decline in CD4 cell count. Both parameters are highly indicative and predictive but cannot be used to decide to which drug a patient should be switched for further effective drug combination.

**Cost effectiveness**

Determining the cost effectiveness of ARV treatments is an ethical question involving assessments of the value of an individual human life and the value of prolonging that life under improved conditions. Although individuals alone are not qualified to make this judgement, priorities in specific settings can be made.

Depending on viral fitness (aggressivity of viral growth over time) and on the rest of the immune function, a patient under appropriate treatment with at least three drugs, two for inhibition of the RT and one for the PR, may benefit from the therapy for nine months and, on the basis of what is known today, longer than two years. More cannot yet be claimed as no patient has received triple therapy for longer than 2 years.
The cost of these drugs is around US$ 1000 per month. This does not include costs of additional treatment of opportunistic infections and other problems such as diarrhoea, nor the costs of monitoring.

The costs for laboratory examinations every three months are as follows:

- US$ 100 viral load
- US$ 40 CD4 cell count
- US$ 5 blood cell examination

per patient, assuming that equipment is provided and financed by the laboratory. Laboratory monitoring must start with the onset of therapy and has to be continued for as long as the patient is alive or treatable.

The cost of drugs and laboratory tests has to be weighed against per capita income and the economic burden that such treatment represents for families caring for a person living with HIV/AIDS. The cost also has to be weighed against that of antibody screening assays used in bloodbanks to avoid transmission of HIV to transfused patients and later, possibly their sexual partners. It also has to be weighed against equipment used for vaccination and injection procedures.

Set up and operation of laboratory facilities for the monitoring of HIV infected patients

The initial investment for a fully equipped laboratory is between US$ 150,000 and 300,000. This is a substantial investment that can be made in association with other institutions; many countries are likely to have only one or two such facilities nationally. Additionally yearly running costs of US$ 10,000 have to be budgeted. Staff training is another expense to be added and training should be repeated every two years so that the laboratory adheres to international standards and is accepted for reference purposes. Preferably, the training laboratory should have the same climatic conditions as the laboratory requesting training.

The potential for international cooperation exists. For example, laboratory facilities can be operated through university based cooperation or National Agency based cooperation (CDC, MRC, GTZ). They can link up with, and contribute to basic research on the characterization of the HIV strains currently prevalent, emerging or spreading, their resistance patterns, their pathogenic action and patients' genetic patterns, as for example in the investigation of natural resistance markers in the Nairobi sex workers who have had multiple exposures to the virus and yet are not infected.
References

1. Sninsky JJ, Kwok S. The application of quantitative polymerase chain reaction to therapeutic monitoring. AIDS 1993; 7 (suppl 2) S29-S34.


Setting Priorities for Government Involvement with Antiretrovirals

Nicholas Prescott*

Editors’ note: The author of this paper uses the treatment of HIV/AIDS with AZT monotherapy as a possible scenario for costing purposes only. This should not be interpreted as an endorsement of monotherapy for the treatment of HIV infection.

Introduction

This paper examines four questions posed by economic analysis to help set priorities for government involvement with antiretroviral therapy for people living with HIV/AIDS. The main focus is on making decisions about policy relating to ARVs in developing countries where the needs are greatest and resource constraints are most binding. While the answers may vary considerably depending on individual country circumstances, the analytical foundations for setting priorities are the same. First, how does antiretroviral therapy link to broader health sector and country development objectives? Second, what other interventions need to be considered including the various ARV treatments? Third, which of these alternatives are realistically affordable given the country’s resource constraints? And fourth, which of the affordable alternatives are most efficient in achieving a favourable development impact?

Linkage to development objectives

Any consideration of government involvement with antiretroviral treatment for HIV/AIDS needs to start with a clear view of how such treatment links to broader health sector strategy and country development goals. Despite its terrible human toll, HIV/AIDS is only one of many health problems facing developing countries. And health improvement is only one of many pressing development challenges involved in raising people’s living standards – from reducing illiteracy, to providing infrastructure and expanding job opportunities. Looking at this linkage just in terms of improving health requires an epidemiological assessment of the magnitude of ill-health due to HIV/AIDS relative to other health problems – not only its importance today but also its significance tomorrow as morbidity and mortality from the epidemic continues to grow. A suggestive indicator of these relative magnitudes is the burden of disease due to disability and premature death from different causes. Recent estimates of the global burden of disease expressed in terms of the number of years of healthy life lost (Murray & Lopez, 1996) suggest that for developing countries:

- in 1990 – HIV/AIDS ranked as the 26th leading cause, contributing just 0.84% of the total disease burden. Lower respiratory infections ranked first with a share of 9.07%.
- in 2020 – HIV/AIDS will move up to 10th place, accounting for 2.61% of the disease burden. Meanwhile the leading cause of ill-health will become ischaemic heart disease, contributing 5.93% of the total disease burden.

These global estimates illustrate the magnitude of the health problem which antiretroviral treatment aims to address, while at the same time emphasizing the likely tradeoffs with other health problems of arguably greater magnitude. How much difference antiretroviral treatment could make to improving overall health therefore depends on the relative contribution of HIV/AIDS to ill-health in specific country circumstances. Defining the strength of this link obviously requires a quantitative assessment of epidemiological magnitudes -- numbers of people who are asymptomatic, symptomatic and living with AIDS -- in the particular countries concerned. This in turn sets the stage for analyzing alternatives for government involvement with antiretrovirals.

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Analysis of alternatives

Comparing alternative ways of addressing the HIV/AIDS problem – different types of antiretroviral treatment, along with other preventive interventions -- will help decision makers choose the option most likely to achieve development objectives. It is not enough to think of the choice set just in terms of the technical options -- in practice the consideration of alternatives must also examine alternative target groups, as well as public or private sector alternatives in both provision and financing.

First, technical alternatives – innovations in antiretroviral treatment have greatly expanded the choice set to include a wide range of different drug regimes involving reverse transcriptase and protease inhibitors, that can be given singly or as combination therapies, with widely different implications for unit costs and clinical outcomes.

Second, target groups are also different even with the same technical option – ranging from people with AIDS, to symptomatics or asymptomatics, as well as infected pregnant women. The different population sizes involved have major implications for the aggregate costs of treatment, as well as its likely effectiveness in reducing the burden of disease. For example, Thailand’s population of 58 million was estimated to have a nationwide pool of some 746,000 infected adults in 1996 – including a caseload of around 47,000 adults with AIDS, plus another 61,000 symptomatics, and 22,000 infected pregnant women.

Third, whether antiretrovirals are or could be provided by the private sector instead of the public sector needs to be examined carefully. Is there a private market for antiretrovirals, or is there a private sector delivery system that could provide them? If so public provision of antiretrovirals might induce substitution of patients seeking treatment out of the private sector, thus lowering the net impact of public sector provision.

Finally, is there any rationale for public financing of antiretroviral treatment instead of relying on private payments? One important justification for public subsidies involves interventions that generate epidemiological externalities – where antiretroviral treatment prevents transmission of infection to others. The externality argument clearly does apply to preventing maternal-child transmission (MCT). But it does not seem to apply to using antiretrovirals to treat other infected groups -- unless viral load is eliminated, as has been suggested with protease inhibitors.

A different justification for subsidizing antiretroviral treatment is that government policy generally does provide subsidies to help insure against catastrophic financial risks due to ill-health. But then governments should be consistent in applying their particular national price/subsidy policy across all diseases -- without discriminating in pricing policy between people with HIV and people with other conditions. Granting preferential subsidies to patients with HIV/AIDS risks crowding out uninfected patients that might get more health benefits from the fixed amount of available subsidies.

Affordability

Analyzing the financing options for antiretrovirals leads straight into the affordability question that is of such importance in low and middle-income developing countries. Policymakers need to reject alternatives for government involvement that are not financially affordable – otherwise they will get locked into unsustainable policies that undermine the objectives of getting involved in the first place. This means focusing on the subset of antiretroviral alternatives that are affordable from the point of view of those who have to finance the relevant costs – government and households.

The distribution of treatment costs between these parties depends on two factors -- the choice of pricing policy, and its interaction with the relevant budget constraints. Estimates from Thailand
illustrate these factors in the context of a middle-income country with a per capita income of USD 2,410 in 1994 (Prescott et al., 1996). Figure 1 shows the estimated unit costs of treatment expressed in Thai baht (approx. 25 baht per USD), together with the associated prices/subsidies for a range of ten treatment options for HIV/AIDS. Eight of these regimes involve administration of antiretroviral drugs, not including the new protease inhibitors:

- Model A1: adult AIDS -- universal coverage of optimal OI treatment
- Model A2: adult AIDS -- zidovudine (ZDV) monotherapy
- Model A3: adult AIDS -- ZDV/ddI or ddC sequential monotherapy
- Model A4: adult AIDS -- ZDV/ ddI or ddC combination therapy
- Model A5: adult asymptomatic HIV -- ZDV monotherapy
- Model A6: adult asymptomatic HIV -- ZDV/ ddI or ddC sequential monotherapy
- Model A7: adult asymptomatic HIV -- ZDV/ ddI or ddC combination therapy
- Model A8: adult asymptomatic HIV: ZDV monotherapy
- Model C1: MCT: formula feeding
- Model C2: MCT: ZDV plus formula feeding

Figure 1:
Pricing Policy
in baht per case year, at 1995 prices

Expressed in equivalent USD the unit costs of treatment for adults with AIDS range from about USD 2,000 per patient-year with zidovudine monotherapy (model A2) to USD 4,000 per patient-year with zidovudine/ddI or ddC combination therapy (model A4). The annual unit costs of treatment for symptomatic and asymptomatic target groups appear lower because these earlier stages in the life cycle of treatment involve fewer provider visits and OI drugs – but later progression to AIDS will raise unit costs. Meanwhile the unit cost of treating pregnant women following the ACTG076 protocol is only
about USD 500 per mother-child pair (model C2). The pricing policy regime superimposed on these costs provides free – fully subsidised – antiretrovirals to patients, while requiring around one-third cost recovery for OI drugs and inpatient/outpatient services. This subsidy structure reduces patient costs during AIDS to less than USD 500 per year.

Whether such a subsidy policy is affordable from the government’s point of view depends on the ratio of fiscal requirements to the projected budget constraint. Here the relevant budget constraint is assumed to be equal to the entire budget allocated to the National AIDS Programme. Options with index values greater than 100 are not affordable. Figure 2 shows the simulations assuming maximum utilization generated by universal coverage and perfect compliance. Under the assumed combination of pricing policy and fiscal constraints all the treatment options involving antiretrovirals appear unaffordable – with the notable exception of preventing perinatal transmission, which has an affordability index of less than 20%. Just treating OIs (model A1) for the projected number of AIDS patients would exhaust the whole budget, without adding any antiretroviral drugs.

Figure 2:
Fiscal Impact: Subsidy/Budget Ratio
National AIDS program = 100

To assess affordability of this pricing policy from the patients’ point of view, it is important to think in terms of the distribution of incomes -- or its proxy, per capita consumption expenditure (PCE) -- instead of the average level of income in the whole population. Figure 3 shows the cumulative distribution function for three different categories of PCE – medical care, nonfood expenditure and total consumption. The vertical axis shows the annual amount of PCE, while the horizontal axis shows the proportion of the total population. Suppose, for example, that average nonfood expenditure represents a realistic budget constraint on patients’ ability to pay for HIV/AIDS treatment. Then the subsidised price of antiretroviral treatments for adults with AIDS -- around 9,000 baht or USD 500 from Figure 1 -- seems unaffordable for around 50% of the whole population, while still being affordable for the rest.
Efficiency

These empirical examples from Thailand – a middle-income developing country – suggest that large-scale programmes of antiretroviral treatment may not be easily affordable either from the fiscal standpoint of governments or by many private households, except for prevention of perinatal transmission.

Efficiency considerations point in the same direction as affordability. Figure 4 shows the simulations of effectiveness based on optimistic estimates of clinical efficacy, and assuming perfect patient compliance and universal coverage -- in practice, however, one might expect programme coverage and compliance rates to be much less than 100%. Effectiveness is measured in terms of the proportionate reduction in the burden of disease due to HIV/AIDS -- or gain in quality-adjusted life years (QALYs) -- that can be attributed to different treatment options. The simulations suggest, first, that the potential effectiveness of antiretroviral treatment options – excluding protease inhibitors – is clustered around 10-15% of the baseline disease burden. And second, the effectiveness of preventing perinatal transmission may be nearly as high as treating adults.
Putting these effectiveness estimates together with the cost figures makes it possible to compare the cost-effectiveness of antiretroviral alternatives (Figure 5). The adult antiretroviral regimes generate around 30 QALYs per million baht of expenditure. In contrast, preventing perinatal transmission appears to produce more than 600 QALYs per million baht – a twentyfold difference.

References


Cost and Financing
Aspects of Providing Antiretroviral Therapy

Katherine Floyd and Charles Gilks

Editors’ note: The authors of this paper use the treatment of HIV/AIDS with AZT monotherapy as a possible scenario for costing purposes only. This should not be interpreted as an endorsement of monotherapy for the treatment of HIV infection.

Introduction

When the HIV/AIDS epidemic was first recognised in the early 1980s, treatment options for HIV-infected people were limited. While prophylaxis was available for some AIDS-associated opportunistic infections such as tuberculosis and pneumocystis carinii pneumonia, therapies which had been demonstrated to affect the behaviour of the virus itself were not available. Following approval by the USA’s Food and Drug Administration in 1987, the prescription of AZT to AIDS patients became common medical practice, especially when controlled trials showed it was an effective antiretroviral agent and that it lengthened life expectancy. It became common medical practice to prescribe AZT (now called zidovudine) to HIV-infected patients who had not yet developed AIDS, both to patients who had HIV-related symptoms and to those who were asymptomatic (Coser and Lambrinos, 1992). The drug is widely used in North America, Europe and Australia, in combination with a number of other antiretrovirals (ARVs) which have now entered the market.

In contrast, ARVs are not yet widely available to HIV-infected people or AIDS patients in developing countries. While there are notable exceptions such as Thailand, in most countries of Africa, Asia, Latin America and the Caribbean, access to AZT and the newer drugs is only possible through the private sector (Santos et al, 1994). As the HIV epidemic worsens in these regions, policy development in the area of antiretroviral therapy is increasingly warranted. This is especially so in light of recent suggestions that antiretroviral combination therapies may not only prolong life but may even, if taken for life, be capable of preventing HIV-infected people from progressing to AIDS at all (Piot 1996); and evidence that provision of AZT to pregnant women reduces transmission to their children (Connor et al, 1994). In addition, with rising rates of infection among hospital patient populations, demand for AZT prophylaxis from health workers exposed to HIV is likely to increase.

The economic aspects of providing ARVs to HIV-infected people and exposed health workers are one of a number of important considerations which should be analysed to help inform policy development. This paper addresses such aspects and is divided into seven sections as follows:

1. Cost of providing antiretroviral therapy, in which data on the cost of the drugs is provided and evidence concerning other costs associated with provision of therapy is summarized;
2. Total cost implications of providing antiretroviral therapy, in which the cost data presented in (1) are used in combination with region-specific data concerning the number of people with AIDS or HIV infection to estimate the total costs for different geographic regions of providing therapy;
3. Total cost implications of providing antiretroviral therapy in comparison with available resources, in which region-specific GDP, health sector expenditures, National AIDS Programme budgets, and official development assistance are compared with the estimates for total costs of antiretroviral therapy given in Section 2;

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4. Cost-saving potential and cost-effectiveness of antiretroviral therapy, in which evidence concerning the impact of ARVs on health system resource use and life expectancy are used in combination with estimates of the costs of medical care for HIV/AIDS to assess whether, despite the costs associated with their provision, ARVs might be either cost-saving or cost-effective;

5. Cost, cost-saving potential, and cost-effectiveness of providing AZT therapy to pregnant women, in which available data concerning the costs associated with providing AZT to pregnant women, the potential for cost-saving due to averted paediatric AIDS cases, and likely cost-effectiveness where therapy may not be cost-saving are discussed;

6. Cost and cost-effectiveness of prophylaxis for health care workers, and

7. Financing antiretroviral therapy, in which alternative financing options are assessed.

Cost of providing antiretroviral therapy

Available data concerning the costs of providing ARV therapy are presented in two separate sections: Section 1 presents the costs of ARVs themselves and Section 2 presents the other costs associated with providing ARVs. Section 3 highlights other costs which may be important, especially in developing countries.

Antiretroviral drug costs

The cost of the ARVs themselves are shown in Table 1 below. The most recent figures suggest that, at market prices, AZT costs US$ 1.50/100mg tablet. Since the standard regimen involves 500mg/day, this means that the daily per patient cost is US$ 7.50, the average monthly cost per patient is US$ 228, and the annual cost per patient is US$ 2 738. This is considerably less than in the late 1980s, when the annual per patient cost of AZT was reported to be US$ 10 000 (Sabatier et al, 1989).

Table 1: Antiretroviral Drug Costs (US$) at Market Prices

<table>
<thead>
<tr>
<th>Drug and dosage required</th>
<th>Unit Cost</th>
<th>Monthly Cost</th>
<th>Annual Cost</th>
<th>Source, Date of Data and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (AZT) 250mg twice per day</td>
<td>1.50 per 100mg</td>
<td>228</td>
<td>2 738</td>
<td>USA, 1994, Bozette et al; Mauskopf et al, 1996</td>
</tr>
<tr>
<td>didanosine (ddl) 200mg twice per day</td>
<td>1.44 per 100mg</td>
<td>175</td>
<td>2 102</td>
<td>USA, 1991, Hellinger 1992</td>
</tr>
<tr>
<td>zalcitabine (ddC) 0.75mg three times a day</td>
<td>2.40 per 0.75mg</td>
<td>220</td>
<td>2 640</td>
<td>World wide web page of AIDSRx, a North Carolina, USA based company, 1997</td>
</tr>
<tr>
<td>stavudine (d4T) 40mg twice a day</td>
<td>3.90 per 40mg</td>
<td>232</td>
<td>2 788</td>
<td>As above</td>
</tr>
<tr>
<td>lamivudine (3TC) 150mg twice daily</td>
<td>3.60 per 150mg</td>
<td>214</td>
<td>2 572</td>
<td>As above</td>
</tr>
<tr>
<td>ritonavir 600mg twice daily</td>
<td>11.50 per 600mg</td>
<td>692</td>
<td>8 308</td>
<td>As above</td>
</tr>
<tr>
<td>saquinavir 600mg three times a day</td>
<td>6.10 per 600mg</td>
<td>545</td>
<td>6 540</td>
<td>As above</td>
</tr>
</tbody>
</table>

1 approved in 1991 in the USA to treat patients who cannot tolerate AZT (Hellinger 1992)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Annual Treatment Cost</th>
<th>Negotiated Annual Treatment Cost as a % of Annual Treatment Cost at market prices</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>776</td>
<td>28%</td>
</tr>
<tr>
<td>saquinavir</td>
<td>4 340</td>
<td>66%</td>
</tr>
<tr>
<td>ritonavir</td>
<td>5 528</td>
<td>67%</td>
</tr>
<tr>
<td>lamivudine</td>
<td>2 108</td>
<td>82%</td>
</tr>
</tbody>
</table>

Meanwhile, three of the newer nucleoside reverse transcriptase inhibitors (NRTIs) are slightly cheaper (didanosine costs US$ 175 per month, zalcitabine US$ 220 per month, and lamivudine US$ 214 per month), while a fourth - stavudine - is slightly more expensive at US$232 per month. The even more recent protease inhibitors are considerably more: ritonavir costs US$692 per month, saquinavir US$ 545 per month, and indinavir US$ 533 per month. The one non-nucleoside reverse transcriptase inhibitor - nevirapine - is at the lower end of the spectrum of costs, at US$ 272 per month. Double combination therapies range in costs from US$ 403 to US$ 773 per month, while the triple combination therapies range from US$ 662 to US$ 993, increasing to up to US$ 1465 if ritonavir is added.

These costs are substantial. However, it is important to note that large reductions in these costs may be possible when drugs are purchased in bulk. To illustrate this, Table 2 below shows the drug costs which have been negotiated in Uruguay on the basis of bulk-purchase (Abreu, personal communication). This shows that annual treatment costs, approximately two-thirds of those quoted above, have been achieved for two of the drugs, and the cost of AZT has been reduced to 28% of the US market price quoted above.

Table 2: Drug costs (US$) in Uruguay when drugs are purchased in bulk

<table>
<thead>
<tr>
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</table>

2 see Drug and Therapeutics Bulletin Vol. 35 No. 4 April 1997
3 see Drug and Therapeutics Bulletin Vol. 35 No. 4 April 1997
Non-drug costs involved in providing ARV therapy

In addition to drug costs, other important costs associated with providing therapy include: HIV tests to establish whether someone is HIV+ and hence eligible for therapy; pre- and post-test counselling; regular out-patient visits to monitor patients for side-effects and to issue supplies of drugs; laboratory tests such as CD4 counts, complete blood counts, viral loads, and chemistry panels to monitor patient health status; and out-patient visits/hospitalizations associated with adverse drug effects. Few data are available concerning their cost. Those cost data which could be accessed are shown in Table 3.

Table 3: Non-drug costs associated with providing antiretroviral therapy (US$)

<table>
<thead>
<tr>
<th>Cost Item</th>
<th>Unit Cost</th>
<th>Source, Date of Data and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count*</td>
<td>157</td>
<td>USA, 1995, Gable et al</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>JCRC, 1997, Uganda</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>USA, 1991, Schulman et al</td>
</tr>
<tr>
<td>Viral load test</td>
<td>163</td>
<td>Gotch, 1997, personal communication</td>
</tr>
<tr>
<td></td>
<td>133</td>
<td>JCRC, 1997, Uganda</td>
</tr>
<tr>
<td>Complete blood count**</td>
<td>2</td>
<td>USA, 1995, Gable et al</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>USA, 1996, Gorsky et al</td>
</tr>
<tr>
<td>Chemistry panel***</td>
<td>12</td>
<td>USA, 1991, Schulman et al</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>USA, 1996, Gorsky et al</td>
</tr>
<tr>
<td>Serum amylase</td>
<td>18</td>
<td>USA, 1995, Gable et al</td>
</tr>
<tr>
<td>Transfusion for AZT-induced anaemia</td>
<td>580</td>
<td>USA, 1995, Gable et al</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>USA, 1994, Mauskopf et al</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>USA, 1996, Gorsky et al; JCRC, 1997, Uganda</td>
</tr>
<tr>
<td>Rapid HIV Test (Capillus)</td>
<td>3</td>
<td>South Africa, as above</td>
</tr>
<tr>
<td>Rapid HIV Test (Abbot)</td>
<td>10</td>
<td>South Africa, as above</td>
</tr>
<tr>
<td>Pre-test/post-test Counselling Visit for HIV-person</td>
<td>22/33</td>
<td>USA, 1994, Mauskopf et al</td>
</tr>
<tr>
<td>Pre-test/post-test Counselling Visit for HIV+ person</td>
<td>22/77</td>
<td>As above</td>
</tr>
<tr>
<td>Test + counselling</td>
<td>18/12</td>
<td>Uganda 1992/96, quoted in Mansergh et al</td>
</tr>
<tr>
<td>Out-patient visit* (N.B. This is an average OPD visit cost, not specific to ARV therapy-related)</td>
<td>120</td>
<td>USA, 1991, Hellinger</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>USA, 1995, Gable et al</td>
</tr>
<tr>
<td>Day in hospital (N.B. Figures are not for hospital care related to ARV usage. They are included here for guidance only. The USA figure is an average for an AIDS patient; costs for Malawi and South Africa are for TB patients; the Thailand figure is an average for all patients)</td>
<td>1150</td>
<td>USA, 1995, Gable et al</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Malawi, 1995, Sawert</td>
</tr>
</tbody>
</table>

* assumed to be required once/month by Bozette et al and quarterly by Schulman et al
** assumed to be required once/month by both Bozette et al and Schulman et al
*** assumed to be required quarterly by Schulman et al
Other costs which may be important, especially in developing countries

There are some additional costs which may be involved in providing ARV therapy, especially in developing countries, and it is worth highlighting these. Many of the costs quoted in Table 3 above are based on US cost data, where the costs of shipping equipment and supplies will be relatively low because they can be domestically produced. In developing countries where these items will probably have to be imported from countries a considerable distance away, costs are likely to be higher.

In addition, in developing countries, laboratories may have to be strengthened considerably if they are to be capable of providing the diagnostic and monitoring support necessary for provision of ARV therapy. This could include installation of air-conditioners and back-up generators to cope with electricity cuts, and proper maintenance contracts. Developing such capacity may have large costs attached to it.

Total cost implications of providing antiretroviral therapy

The unit costs presented in Section I can be used to estimate what the annual per patient cost of providing ARVs might be. While the drug costs are fairly uniform among countries and will only differ according to freight/customs charges, the costs of the non-drug components are likely to vary substantially - as the costs for a day in hospital shown above indicate. Since most of the non-drug cost data are from the USA, cost estimates for other countries cannot be very precise. This problem is aggravated by the fact that approaches to case management are not well defined for many countries - for example the frequency and type of laboratory tests which would be appropriate, how often monitoring visits would be required, etc. This makes costing difficult, since the required resource inputs cannot be clearly identified.

Moreover, a portion, perhaps even a majority, of patients will not be able to tolerate the drugs, will suffer adverse effects (Hay et al, 1988), will decline to take them at all (Alcorn 1995), or will abandon them after a length of time. This means that the cost of treating patients who suffer adverse effects may be either more or less than the cost of treating patients who suffer no such effects. More, if they persevere with treatment and have to consult and be treated for adverse effects; less if they abandon or decline treatments.

Due to these difficulties, a simplified cost analysis is given here. The annual cost for a patient receiving ARV is assumed to be the cost of the drugs, the cost of four outpatient visits (with a range from $1 to 120), the cost of four complete blood cell counts (with a range of $2 to 21), four CD4 counts (with a range from $30 to 157), four viral load tests (a frequency suggested in the minutes of the February 26th 1997 meeting of the HIV Physicians Forum for the North West Region in the UK) at US$163 each, and four chemistry panels (with a range from $12 to 35). The range in costs for the final three components reflects the range shown in the Table 3 cost data. The range in outpatient costs uses the highest figure for the USA shown in Table 3 as an upper estimate, but US$1 is used as a lower estimate since the day-in-hospital cost for Malawi suggests that in very poor countries this may be a realistic figure. Counselling costs and HIV test costs are ignored since these are one-off costs and are minor in comparison with other cost components. The cost impact of adverse effects is also ignored since there are so few data which can provide guidance. However, it is worth noting that in the USA it has been suggested that adverse effects will substantially increase ARV therapy costs (Bozette et al, 1994). It has also been suggested that outpatient costs for HIV-infected people are higher than those for non-infected patients (McDermott et al, 1991), and both the minimum and maximum estimates used here may therefore underestimate the cost of an OPD visit for patients receiving ARV which would be incurred in practice.
Using the above assumptions, the per patient annual cost for ARV therapy would range from US$ 3570 to US$ 4722 for AZT therapy, and from US$ 8776 to US$ 13 902 for triple-combination therapy (excluding a regimen which includes ritonavir). It is noteworthy that the drugs constitute between 58% and 77% of total per patient annual costs with AZT therapy, and between 86% and 91% of total per patient annual costs with triple combination therapy. This shows that if drug costs can be reduced, as has already happened with AZT, and as Uruguay has demonstrated, therapy may become significantly cheaper. Partnerships among international agencies, individual governments and drug companies may also reduce costs. However, at current market prices, even the cost of AZT therapy is higher than average annual incomes in most countries.

To estimate the total annual cost which would be incurred if ARV therapy were to be provided in different geographic regions, these figures are then used in combination with 1996 data concerning the number of people with HIV infection but not AIDS, and the number of people with AIDS (taken from figures quoted in Mann and Tarantola, Chapter 1, 1996). Two scenarios are presented. In the first, everyone receives ARV therapy. Though unrealistic, this is useful in providing an upper total cost estimate. In the second, 50% or those eligible are assumed to receive therapy. The results are shown in Table 4 below. When considering these figures, it is worth bearing in mind that it has been calculated that implementation of six major prevention strategies in developing countries would in total cost between US$ 1.5 and US$ 2.9 billion (Broomberg and Schopper, 1996).

Table 4: Estimated total annual costs (US$) for ARV therapy by geographic region under alternative assumptions in 1996

<table>
<thead>
<tr>
<th>Geographic Region</th>
<th>Estimated Number of People with AIDS in 1996</th>
<th>Estimated Number of People with HIV infection but not AIDS in 1996</th>
<th>Estimated Total Cost for AZT therapy if 50% of those eligible receive it</th>
<th>Estimated Total Cost for triple-combination therapy if 50% of those eligible receive it</th>
<th>Estimated Total Cost for AZT therapy if 100% of those eligible receive it</th>
<th>Estimated Total Cost for triple-combination therapy if 100% of those eligible receive it</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>91 000</td>
<td>837 000</td>
<td>1.65 to 2.2 billion</td>
<td>4.1 to 6.5 billion</td>
<td>3.3 to 4.4 billion</td>
<td>8.1 to 12.9 billion</td>
</tr>
<tr>
<td>Western Europe</td>
<td>52 000</td>
<td>642 000</td>
<td>1.25 to 1.65 billion</td>
<td>3 to 4.8 billion</td>
<td>2.5 to 3.3 billion</td>
<td>6.1 to 9.6 billion</td>
</tr>
<tr>
<td>Oceania</td>
<td>2 000</td>
<td>23 000</td>
<td>0.04 to 0.06 billion</td>
<td>0.1 to 0.2 billion</td>
<td>0.09 to 0.1 billion</td>
<td>0.2 to 0.35 billion</td>
</tr>
<tr>
<td>Latin America</td>
<td>61 000</td>
<td>976 000</td>
<td>1.85 to 2.45 billion</td>
<td>4.6 to 7.2 billion</td>
<td>3.7 to 4.9 billion</td>
<td>9.1 to 14.4 billion</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>803 000</td>
<td>10 809 000</td>
<td>20.7 to 27.4 billion</td>
<td>50.9 to 80.7 billion</td>
<td>41.5 to 54.8 billion</td>
<td>101.9 to 161.4 billion</td>
</tr>
<tr>
<td>Caribbean</td>
<td>19 000</td>
<td>343 000</td>
<td>0.65 to 0.85 billion</td>
<td>1.6 to 2.5 billion</td>
<td>1.3 to 1.7 billion</td>
<td>3.2 to 5 billion</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>2 000</td>
<td>30 000</td>
<td>0.06 to 0.08 billion</td>
<td>0.15 to 0.2 billion</td>
<td>0.1 to 0.15 billion</td>
<td>0.3 to 0.4 billion</td>
</tr>
</tbody>
</table>

*see Appendix 1 for a list of the countries included in each geographic region*
Total cost implications of providing antiretroviral therapy in comparison with available resources

The total costs associated with providing ARVs would be substantial in absolute terms (Table 4). However, it is important to consider these costs in the context of available resources. Table 5 below illustrates how the total costs discussed in Section 2 compare with GDP, health sector expenditure, and National AIDS Budgets in the different geographic regions. The lower estimate represents the situation illustrated in Table 4 in which 50% of those eligible receive ARV monotherapy at the lowest estimated annual cost of AZT therapy (US$3 570 per patient); the higher estimate represents the situation illustrated above in which 100% of those eligible receive triple-combination therapy at the highest estimated annual cost for such therapy (US$13 902 per patient).

Table 5: Estimated Total Annual Cost for ARV Therapy as a percentage of GDP, Health Sector Expenditures, and National AIDS Budgets by Geographic Region

<table>
<thead>
<tr>
<th>Geographic Region</th>
<th>Estimated Annual Cost of ARV Therapy as % 1991 GDP</th>
<th>Estimated Annual Cost of ARV Therapy as % 1990 Total Health Expenditures</th>
<th>Estimated Annual Cost of ARV Therapy as % National AIDS Budgets</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>0.03 to 0.2</td>
<td>0.2 to 1.8</td>
<td>31 to 243</td>
</tr>
<tr>
<td>Western Europe</td>
<td>0.02 to 0.1</td>
<td>0.2 to 1.9</td>
<td>1 136 to 8 727</td>
</tr>
<tr>
<td>Oceania</td>
<td>0.01 to 0.1</td>
<td>0.15 to 1.3</td>
<td>57 to 500</td>
</tr>
<tr>
<td>Latin America</td>
<td>0.1 to 1</td>
<td>3.1 to 23.9</td>
<td>93 to 720</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>8.6 to 66.9</td>
<td>215 to 1 673</td>
<td>258 750 to 2 017 500</td>
</tr>
<tr>
<td>Caribbean</td>
<td>1.9 to 14.8</td>
<td>48.1 to 370</td>
<td>92 857 to 714 286</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>0.006 to 0.04</td>
<td>0.15 to 1</td>
<td>750 to 5 000</td>
</tr>
<tr>
<td>SE Mediterranean</td>
<td>0.02 to 0.1</td>
<td>0.4 to 3.5</td>
<td>2 400 to 20 000</td>
</tr>
<tr>
<td>Northeast Asia</td>
<td>0.007 to 0.06</td>
<td>0.2 to 1.5</td>
<td>300 to 2 400</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1.9 to 14.6</td>
<td>46.8 to 364</td>
<td>16 571 to 128 857</td>
</tr>
</tbody>
</table>

These figures suggest that ARV therapy would be unaffordable in sub-Saharan Africa, Southeast Asia, the Caribbean, and Latin America, but could be considered in other regions where total costs would be less than 1% of GDP and less than 4% of health sector expenditure even for the most expensive combination therapies. Overseas Development Assistance (UK) for HIV/AIDS, estimated at US$ 257 million in 1993 (Laws, 1996), is also too small to change this conclusion.

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3 GDP figures from 1991 were used, since these were readily available. Health expenditure data were not readily available, and therefore calculations assumed that, on average, developing countries spend approximately 4% of their GDP on health (World Development Report 1993). Calculations for North America, Western Europe and Oceania were based on 1990 country-specific data reported in the World Development Report 1993. National AIDS Budgets data taken from "AIDS in the World II", eds. Mann and Tarantola 1996, and come from 1992 or 1993. See Appendix 1 for full details of GDP, Actual or Estimated Total Health Expenditure, and National AIDS Budgets.
Cost-saving potential and cost-effectiveness of antiretroviral therapy

Cost-saving potential

Despite the large costs associated with ARVs, it is possible that their provision would actually deliver overall cost-savings through reducing costs associated with HIV-related illnesses. It has been suggested that annual medical care costs for AIDS care per case are in the region of 1 to 4.6 times per capita GNP for any given country (Martin, 1996). Data on costs of caring for HIV-infected prior to development of AIDS are scarce and published data are confined to the USA, Australia and South Africa (Hurley et al, 1995; Hellinger, 1992; Kinghorn et al, 1996; Karstaedt et al, 1996). One study has suggested that costs per year of treating HIV disease are approximately 25% of the costs per year of treating a person with AIDS.

Triple-combination therapies

This means that if triple combination therapies were to succeed in preventing HIV-related illnesses, costs saved in any year would be a maximum of 4.6 times per capita income. They would then be cost-saving for the health system over the expected period of HIV/AIDS illness in any country with a per capita income of US$ 1908 (if the annual per patient cost was US$ 8776) to US$ 3022 (if the annual per patient cost was US$ 13 902 per year). The majority of countries do not have such high incomes - for example Thailand, a relatively wealthy newly industrializing country, had an average per capita income of US$ 1570 in 1991 (World Development Report, 1993); and most African countries have average per capita incomes of less than US$1 000, with many below US$ 500 (World Development Report, 1993).

If annual costs for care of HIV/AIDS related illnesses were equivalent to per capita incomes (most cost data suggest this to be a more realistic figure even for AIDS care, with pre-AIDS care having a much lower cost where it has been measured: the higher estimates were from the early years of the epidemic when more care was provided in tertiary facilities and doctors were less familiar with HIV/AIDS-related health problems), therapies would only be cost-saving over the expected period of HIV/AIDS illness, from the health system’s perspective, in countries with average per capita incomes of at least US$ 8776. Moreover, cost-savings would be unlikely in the long-run, since therapy costs might have to be incurred for many years or even for life, while medical care costs for illness would extend for only the more limited period from infection to death. Very few countries have incomes as high as US$ 8776 per capita, although in those that do, the cost-saving potential of therapies would be enhanced if a societal perspective is taken, since this takes the indirect costs associated with lost income due to illness/early death into account.

In the vast majority of countries where incomes are considerably less than US$ 8776 to US$ 13 902 per year, therapy is very unlikely to be cost-saving even when the wider societal perspective is taken. For example, even in a relatively high-income developing country such as South Africa, where annual per capita incomes are in the region of US$ 2000, medical care costs saved are likely to be approximately US$ 2000 per year for AIDS care (and less for care pre-AIDS). Prevented income losses would be worth US$ 2000 per year. Triple combination therapy would not be cost saving even at the lower cost estimate of US$ 8776 per year. In a very poor country such as Malawi, with a per capita income of US$ 230 in 1991 (World Development Report, 1993) costs saved over the lifetime of HIV/AIDS illness for a given person would be unlikely to match the cost of even one month’s supply of combination therapy drugs.
AZT therapy

Meanwhile, the limited evidence available indicates that AZT monotherapy may initially result in reduced health care costs in comparison with HIV+ individuals not receiving the drug, but that these cost-savings are not sustained for long (Cosler and Lambinos, 1992; Montaner et al, 1989). One study found similar lifetime costs for AIDS patients (Schitoverysky et al, 1990), while others have suggested that both patients with symptomatic HIV illness and AIDS patients receiving AZT incur higher costs than those not receiving the drug over the course of their infection, due to lengthened survival time (Cosler and Lambinos, 1992; Moore et al, 1994).

Cost-effectiveness

While ARV therapy may not be cost-saving, this is true of most health care interventions. The important issue then becomes whether their provision would represent a cost-effective use of resources, for example in terms of the cost per year of healthy life gained, or the cost per quality adjusted life year gained.

AZT therapy

AZT therapy has been reported to prolong life in a variety of studies. For example, it has been reported to increase survival of AIDS patients from a median of 9.6 months to a median of 21.2 months (Elhaggar 1993), from a median of 235 to 605 days (Moore et al, 1994), by an average of between one and two years (Anderson and May, 1992), by eight months (Hay et al, 1988), by 227 days (Santos et al, 1994), between 0.3 and 3.3 discounted life years (Schulman et al, 1991), and by two months (Oddone et al, 1993). The cost per healthy life year gained has been variously estimated at US$ 48 000 (Moore et al, 1994), between US$ 15 043 and US$ 30 641 (Bozzette et al, 1994), between US$ 6 653 and US$ 70 526 (Schulman et al, 1991), and US$ 129 000 (Oddone et al, 1993). At the lower cost range this may represent a cost-effective use of resources in North America or Western Europe, but is unlikely to do so in many other contexts. For comparison, the cost/year of healthy life gained has been estimated to be US$ 46 249 for renal dialysis and US$ 113 087 for coronary artery bypass surgery in the USA (Schulman et al, 1991). In developing countries, the cost/disability-adjusted life year (DALY) has been estimated at US$ 3-5 for short-course tuberculosis chemotherapy, US$ 30-50 for prenatal and delivery care, US$ 1-3 for STD treatment, and US$ 25-30 for the expanded programme of immunization (EPI).

Meanwhile, the European multicentre Concorde trial involving 1749 people followed over a three year period found no difference in progression to AIDS or survival in the AZT vs placebo group. This would suggest the drug is not cost-effective at all.

Triple-combination therapies

The cost/year of healthy life gained would be only US$ 8776 to US$ 13 902 for triple combination therapies if they worked, even before cost-savings due to prevented income losses and avoided medical costs are considered. This would appear to make the intervention relatively cost-effective in developed countries, where many accepted health care interventions cost substantially more than this. They would be unlikely to be cost-effective in many other countries, however, as the above figures for STDs, prenatal and delivery care, immunization, and tuberculosis indicate.
Cost, cost-saving potential, and cost-effectiveness of AZT therapy for pregnant women

Cost

While antiretroviral therapy appears prohibitively expensive in many regions, therapy for HIV infected pregnant women over a relatively short time-period may be more affordable. It may also be cost-effective. In the USA, treating pregnant women with AZT in the ACTG076 study has been shown to reduce maternal-child transmission from a rate of 25.5% to 8.3% (Connor et al, 1994). Treatment consisted of 500mg AZT per day on an out-patient basis, starting treatment between weeks 14 and 34 of gestation and continuing until the onset of labour. During labour, a loading dose of 2mg/kg was given, followed by continuous infusion of 1mg/kg of bodyweight per hour during delivery. In the final phase, new-born infants were treated orally with AZT syrup at 2mg/kg bodyweight every six hours, beginning 8 to 12 hours after birth and continuing for six weeks.

The cost for such treatment per pregnant woman has been estimated at US$ 895 for drugs and US$ 150 for laboratory tests or US$ 1 045 in total (Mauskopf et al, 1996). In addition, there are costs associated with testing and counselling all pregnant women, since this is necessary for identification of pregnant women who should receive the AZT treatment. This was estimated to cost US$ 60 for a woman testing negative and US$ 163 for those who test positive. On the assumption of a prevalence rate among pregnant women of 1.71%, testing would on average cost US$ 62 per pregnant woman. AZT treatment for HIV+ pregnant women would on average cost US$ 80 per pregnant woman. With around 4 million births per year (World Development Report, 1993), this represents an annual cost of approximately US$ 318 million or US$ 0.3 billion. In the context of health expenditures in the region of US$ 690 billion per year, this appears affordable. For high income countries with lower prevalence rates than those found in the USA, such treatment also appears affordable.

In poorer countries with higher prevalence rates, these costs appear very high. For example, in Uganda there are an estimated 884 000 births per year (World Development Report, 1993). Drug costs alone would be US$ 79.1 millions, even assuming only 10% of women were HIV+. Total health expenditure in 1990 was only US$ 95 millions (ibid.). It is therefore not surprising that the one published article concerning AZT for pregnant women in sub-Saharan Africa has concluded that the treatment regimen used in the USA trial is too expensive for developing countries (Mansergh et al, 1996). Instead a shorter regimen, of as yet unproven efficacy has been suggested as more realistic. Trials currently underway in Thailand and sub-Saharan Africa will, when completed, demonstrate whether shorter and cheaper regimens are as effective.

Cost-saving potential and cost-effectiveness

In the USA, it has been suggested that AZT therapy for pregnant women is not only affordable but also cost-saving, due to averted paediatric HIV/AIDS treatment costs, which are very large (Mauskopf et al, 1996; Gorsky et al, 1996). In the first study, a child infected by its mother was estimated to incur HIV/AIDS-related health care costs of US$ 98 915. In developing countries, paediatric HIV/AIDS costs are much lower and are unlikely to offset the costs associated with AZT therapy - even when the indirect costs associated with lost productivity are considered (Mansergh et al, 1996). Furthermore, even assuming a less costly treatment regimen than the one shown to be effective in the USA, and making assumptions concerning its likely effectiveness, the cost per HIV infection averted in the baseline analysis was US$ 1 115 (ibid). The authors commented that “This figure would be considered highly cost-effective from a developed country perspective; in a developing country setting in which health care expenditures are much more limited, one might question the cost-effectiveness of this program”. Again, more definitive answers concerning the cost-effectiveness of AZT therapy in
developing countries will be available when trials now underway in Thailand and sub-Saharan Africa are completed.

**Cost and cost-effectiveness of prophylaxis for health care workers**

With rising rates of HIV infection among patients, health care workers (HCWs) are increasingly at risk of contracting HIV through, for example, needlestick injuries. There are at least two prophylaxis options, which have different implications for both cost and cost-effectiveness. These are AZT prophylaxis and triple-combination therapy prophylaxis.

**Prophylaxis with AZT**

AZT prophylaxis involves taking 1000mg per day for four weeks after exposure. At US$ 15/day, the total cost is US$ 420. In addition, at least two HIV tests would be required - one to establish the patient’s HIV status and one to test the HCW’s status after prophylaxis. Counselling may also be considered necessary, and this will incur additional costs.

It has been estimated that there is a 0.3% risk of seroconversion after exposure, although study estimates range from 0 to 1.82% (Allen et al 1992). It has also been recently estimated that prophylaxis reduces this risk by 80% (MMWR June 7, 1996 p468) i.e. to 0.06%. Assuming a 0.3% risk of seroconversion, this means that for every 10 000 health workers who are exposed to HIV but not given prophylaxis, 30 will be infected. With prophylaxis, for every 10 000 health workers exposed to HIV and given prophylaxis, 6 will be infected. Thus for every 10 000 health workers given prophylaxis, 24 infections will be prevented. The cost per prevented infection will be US$ 175 0006. This figure suggests that prophylaxis may only be cost-effective in high-income countries. Moreover, cost-effectiveness in terms of years of life prevented will be further affected by the frequency with which HCWs are exposed to HIV infection: the more the exposures, the higher the chance that a given HCW will become infected and the lower the likely cost-effectiveness of prophylaxis.

**Prophylaxis with triple-combination therapy**

Prophylaxis with triple-combination therapy consists of 200mg of AZT three times a day, 150mg of lamivudine twice a day, and 800mg of indinavir three times a day (MMWR June 7 1996 p 471) for four weeks. The cost of this regimen is US$ 26.40 per day, and US$ 792 for one month. If it is assumed that this regimen would be 100% effective, the cost would be US$ 264 000 per infection averted, making it less cost-effective than AZT prophylaxis.

**Financing antiretroviral therapy**

The high costs associated with antiretroviral therapy mean that traditional approaches to financing care may not be sufficient. The main approaches to health care financing at present include taxation, social insurance systems, private insurance, user fees and community financing schemes. Of these, the high costs at an individual level make cost-recovery through user fees unrealistic. Experience with community financing schemes also tends to indicate that their revenue potential is not large, and mobilizing finance for medical treatment that does not realize individual benefits for everyone would be a significant challenge. Private insurance companies, meanwhile, are in business to make money and as a consequence try to eliminate bad risks. For example, in the USA insurance companies have turned to HIV testing in order to eliminate poor risks from pay pools (Oppenheimer and Padgug, 1986). In South Africa, it has been commented that individual companies are offering lower premiums to people with low HIV/AIDS risk features (Klopper et al, 1993), and in doing so they are likely to force other

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6 i.e. \( (10 000 \times 420) \div 24 = 175 000 \)
companies to do the same in order to remain competitive. This means HIV+ patients find it hard, if not impossible, to obtain coverage; and policies increasingly specifically exclude cover for HIV/AIDS-related health problems. There is even evidence that some cost-conscious employers in the USA have tried to exclude AIDS patients from group insurance policies (Oppenheimer and Padgug, 1986).

It is therefore not surprising that even in the USA, where private insurance is most extensive, AIDS care is largely financed through the public sector. In Maryland, for example, 65% of AIDS patients' care was financed by the programme Medicaid by the time they died (Moore et al, 1994) such that "Medicaid has become the dominant financier of the health care costs of HIV disease". This reliance on Medicaid is supported by other evidence suggesting that 40% of AIDS patients receive care through Medicaid support (Roper and Winkenwerder, 1988). Moreover, in a review of financing policy options by staff at the Harvard AIDS Institute, the major suggestions included mandated workplace insurance, extension of Medicaid eligibility to all those with incomes below the federal poverty level, an opportunity for individuals with incomes to 200% of the poverty level to purchase Medicaid coverage, mechanisms to encourage public and private agencies to pay for continued health insurance after loss of employment, and a shortened waiting period for Medicare disability (Makadon et al, 1990).

This suggests that unless the public sector can afford to provide ARVs, it is unlikely that they will be provided to anything but a small minority of patients financed through other means. Creative, innovative ways of financing care are not in evidence even in North America.

Conclusions

The analysis indicates that high costs are associated with the provision of ARV therapy. The drugs themselves are easily the most important cost component. The large costs associated with therapy, in combination with the number of people eligible for such therapy, appear to make provision of ARVs unaffordable in many parts of the world at present. However, ARV therapy does appear affordable and cost-effective in high-income countries, where it may also be cost-saving when given as prophylaxis to HIV-infected pregnant women. ARV therapy does not appear to be either cost-saving or cost-effective in a developing country context, and this is true for prophylaxis to pregnant women as well as for treatment of HIV-infected individuals. Prophylaxis for health workers does not appear particularly cost-effective in any region. For all except the wealthiest individuals, financing of therapy is likely to depend on public sector provision.

A few notes of caution concerning these conclusions are, however, warranted. It is possible that ARV therapy may become much more affordable in time, as bulk-purchase arrangements become more commonplace, and as partnerships are established among international agencies, governments and drug companies. It is also conceivable that lower drug dosages may be discovered to be as effective as those currently recommended, and that drug companies may be able to reduce their prices once the costs of drug development have been recouped. Nevertheless, the framework of analysis developed here should be useful for informing current policy development, for enabling individual countries to analyse their own current situation vis a vis ARV therapy, and for the generation of cost analyses under different drug cost assumptions.
Bibliography


11. Floyd K., Wilkinson D. and Gilks C.F. Community-based directly observed therapy for tuberculosis: An economic analysis. Corporate Communication Division, South African Medical Research Council, Cape Town, South Africa


16. HIV Physicians forum for the North West Region of the UK. Minutes of meeting February 26th 1997

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76


41. World Bank, World Development Report, 1993
Appendix 1: Countries included in Geographic Regions shown in Tables 4 and 5

North America: Canada, USA  
Western Europe: Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, U.K.  
Oceania: Australia, Fiji, New Zealand, Papua New Guinea  
Latin America: Argentina, Belize, Bolivia, Brazil, Chile, Columbia, Costa Rica, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, Venezuela  
Eastern Europe: Albania, Armenia, Azerbaijan, Belarus, Bosnia, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Poland, Moldova, Romania, Russia, Slovakia, Slovenia, Tajikistan, Macedonia, Turkmenistan, Ukraine, Uzbekistan, Yugoslavia  
Caribbean: Bahamas, Barbados, Cuba, Dominican Republic, Haiti, Jamaica, Trinidad and Tobago  
North-East Asia: Bhutan, Cambodia, China, North Korea, South Korea, Hong Kong, Japan, Laos, Mongolia, Vietnam  
South-East Asia: Bangladesh, Brunei, India, Indonesia, Malaysia, Maldives, Myanmar, Nepal, Philippines, Singapore, Sri Lanka, Thailand  
South-East Mediterranean: Afghanistan, Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Qatar, Saudi Arabia, Syria, Tunisia, Turkey, United Arab Emirates, Yemen

GDP, Actual or Estimated Total National Health Expenditure, and National AIDS Budgets by Geographic Region (US$ billions)

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<tr>
<th></th>
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<tbody>
<tr>
<td>North America*</td>
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<td>6 934.9</td>
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<tr>
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<td>1 503.8</td>
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<td>Southeast Asia**</td>
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Antiretrovirals and their Role in Preventing Mother to Child Transmission of HIV-1

Glenda Gray*

Epidemiology of mother-to-child transmission of HIV-1

Mother-to-child transmission (MCT) of HIV-1 is the main mode of acquisition of HIV infection for children and accounts for over 1 million cases worldwide (1). The majority of these infections occur in sub-Saharan Africa but infection amongst children is increasing rapidly in Asia. The World Health Organisation projects that during the 1990s, between 5-10 million children will be infected as a result of MCT. Estimates of MCT vary from 14%-39% in different regions (2). In Europe the transmission rate is much lower than that reported from Africa, where more than one-third of all children born to HIV-1 positive women become infected.

MCT transmission of HIV-1 can occur prenatally, at the time of delivery, or postnatally through breastfeeding. Evidence for early transmission was documented by the detection of the HIV-1 virus in fetal specimens (3) and by the presence of p24 antigen in fetal serum (4). Transmission occurring at the time of delivery was first based on observations from a study based on twins (5), which found that the first born twin had a two-fold higher risk of contracting HIV-1 than the second born twin. Exposure of the fetus to the virus from the cervico-vaginal secretions was thought to play a role, although the same phenomenon was observed for twins delivered by caesarian section. In addition, recent reports have indicated that mode of delivery may affect the MCT rate. Caesarian section whether elective or emergency has been shown to decrease the risk of transmission (6) and prolonged rupture of membranes (more than four hours) to increase the risk of transmission (7). Postnatal transmission through breastfeeding may explain the higher transmission rate seen in Africa.

The exact contribution of each of these routes to overall transmission has not been quantified but it appears that a substantial proportion of infection occurs at the time of delivery. This conclusion is based on the absence of an HIV-1 dysmorphic syndrome, the lack of manifestations of HIV-1 infection at birth and the finding that HIV-1 is detected in the first week of life in only about 50% of children later proven to be infected (8).

The risk of MCT of HIV-1 is higher in women with clinical, immunological or virological markers of advanced HIV-1 infection. A high viral load has been associated as a key factor in MCT of HIV-1 especially in the viremic phase during primary HIV-1 infection. Recent studies have also found a correlation between viral load and transmission (9). In addition to viral load, the phenotype of the mother’s virus contributes to the risk of MCT (10). Rapid/high virus isolates have been associated with transmitting mothers whereas slow/low virus isolates were associated with non-transmitting mothers. A low CD4 count also correlates with an increased risk of MCT. Immunological factors such as the presence of neutralising antibodies may play a role in minimizing transmission (11). The involvement of specific T-cell immunity in the pathogenesis of MCT has yet to be described.

In summary, MCT appears to be governed by an interaction between viral, immunological and other concomitant factors like the mode of delivery, length of time of rupture of membranes and the practice of breastfeeding. Interventions to reduce MCT of HIV-1 should address these factors.

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Interventions to reduce mother-to-child transmission of HIV-1

Many of the current interventions that are being studied are based on the premise that a substantial proportion of HIV-1 transmission occurs in late pregnancy, during labour and delivery. Studies of interventions to reduce the risk of transmission at this stage include elective caesarian section, disinfection of the birth canal, vitamin A prophylaxis, antiretroviral therapy, formula feeding and passive or active immunization. Presently, the only studies that have been completed with analysis are the ACTG076 study (antiretroviral study) and the study done in Malawi to look at vaginal disinfection of the birth canal in an attempt to reduce intrapartum transmission. Completed studies that are in the analysis stage include the Malawi vitamin A study, a randomized formula feeding study conducted in Nairobi, a self selection study looking at the effects of breastfeeding on MCT in South Africa. Other studies on the effect of vitamin A administration on MCT (South Africa, Zimbabwe and Tanzania), vaginal disinfection (sites in Burkina Faso, Ivory Coast, Kenya), mode of delivery (sites in Europe, South Africa and Brazil) and short course antiretrovirals (see Table 1) are ongoing. Post-partum interventions besides the use of formula feeding have not been studied.

The reduction of MCT transmission of HIV-1 with zidovudine (ZDV) in the ACTG076 study constitutes a major breakthrough, opening new areas for research and interventions in MCT transmission. Antiretroviral therapy may decrease viral load and/or inhibit viral replication in the infant. Results from the ACTG076 study, which looked at the effect of treating the mother with zidovudine during pregnancy, during delivery and treating the infant for the first six weeks of life, support these hypotheses (12). In this randomized placebo-controlled trial in a non-breastfeeding population, treatment with ZDV (100mg 5 times daily) or placebo was started between 14-34 weeks of pregnancy (median 26 weeks). Women also received intravenous ZDV or placebo during labour and the infants received oral ZDV (2mg/kg qid) or placebo for six weeks. All women had CD4 counts >200 per mm3, were symptom-free and were ZDV naive. The first interim analysis on 356 mother-infant pairs demonstrated a rate of MCT of 25.5% in the placebo group, and 8.3% in the ZDV group. Treatment with ZDV achieved a 67.5% reduction in transmission risk. The drug was well tolerated in both the pregnant women and the neonates. The results from the ACTG076 trial and the ZDV in Pregnancy Register show as yet no evidence of teratogenicity or short term adverse effects in the fetus or newborn, but long term follow up is still required.

ZDV has become the standard of care for prevention of perinatal transmission in HIV-1 infected women in North America and Europe. The results of this study show that perinatal transmission can be significantly reduced by the use of antiretrovirals. On the basis of ACTG076 and the recent availability of new classes of antiretrovirals, further reductions in perinatal transmission may be possible in the developed world.

These results may not be applicable to the majority of women in the developing world where the majority of MCT occurs. This is because of the high cost of the intervention (in the USA the regimen costs US$ 1500 per mother-child pair), the logistics of carrying out a regimen that not only requires monitoring of blood parameters and drug reactions, but intravenous infusions during delivery and also treatment to the newborn for six weeks. In addition the intervention needs to be introduced early on in pregnancy, when most women in resource-poor settings book late. Lack of access to counselling and testing in these settings also limits access to antiretrovirals in pregnancy. In addition, the ACTG076 trial was conducted in a non-breastfeeding population so the efficacy of the regimen in a breastfeeding population needs to be determined.

Based on the ACTG076 results, health officials in countries like Brazil and Thailand are implementing the use of antiretrovirals in pregnancy for HIV-1 infected women. Health officials from Brazil announced at the end of March that their government had authorized the allocation of funds to administer ZDV to prevent MCT. Researchers in Brazil are presently planning a trial which will add
ddC to the ACTG076 regimen. Thailand has made available to all pregnant HIV-1 infected women ZDV, ddI and formula milk (for 6 months).

In addition to the issues of affordability and implementability of the ACTG076 regimen, the effect of ZDV in this regimen may have been suboptimal among pregnant women who received more than 14 weeks of therapy, because the initial reduction in HIV viral load induced by ZDV in ZDV naive patients disappears after an average of 14 weeks of treatment to baseline levels, therefore with a shorter regimen, the reduction in perinatal transmission may have been greater. Because all women entering the ACTG076 trial had to have a CD4 count >200, information is required on the efficacy of this regimen in women who have CD4 counts <200.

Current antiretroviral regimens for use in pregnancy

Because of the results of the ACTG076 study, WHO convened an international meeting in June 1994, which recommended that simpler and less costly drug regimens be explored which would be affordable, feasible and sustainable in a poor-resourced setting. Shorter drug regimens include:

1. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, has potent antiretroviral activity and a favourable safety profile. Treatment with nevirapine is associated with the rapid development of drug resistance, which limits the duration of its effect. Therefore its use as a strategy to prevent MCT may be limited to use in labour and delivery. A phase I pharmacokinetics study in 26 mother-infant pairs was started in 1996 in Uganda looking at the use of nevirapine (NVP) in the intrapartum period and postpartum period (child). A similar phase I study is underway in the USA, ACTG 250, which will evaluate the use of NVP in the intrapartum and postpartum period. ACTG 250 will allow the use of ZDV in the study patients. The two studies will complement each other as one will be done in a setting where women breastfeed their babies and another in the USA where breastfeeding amongst HIV-1 infected women is rare.

2. Several short course ZDV trials are underway in developing countries. The ZDV doses vary and most are phase II/III trials. The trials include ZDV as monotherapy (Ivory Coast, Burkina Faso), or ZDV with 3TC (PETRA Study), or ZDV with NVP (Uganda - Phase I PK). Enrolment in PETRA, a UNAIDS multicentred phase III study, is expected to be completed by early 1998.

These studies will provide more information about the exact role that prenatal, intrapartum and postnatal transmission via breastfeeding play in transmission and will also assess the efficacy of short course antiretrovirals in preventing transmission in a predominantly breastfeeding population.

3. A phase I study, ACTG 249, is ongoing in the USA looking at ddl in the prepartum period (oral), intravenous ddl in the intrapartum period, and oral administration of ddl to the child for one week following delivery. ZDV is allowed in the trial.

4. The ACTG 324 trial is a phase I pharmacokinetic study that evaluates the use of oral ZDV in the intrapartum period only.

No information is available regarding infant toxicity or teratogenicity of the other antiretrovirals, including the newer drugs like protease inhibitors. The infants in the ACTG076 study tolerated ZDV well. The only adverse effect seen was a transient anemia. The long-term risks for the child associated with exposure to ZDV in utero and early infancy have not been determined. Concerns related to the potential long-term toxicity of nucleoside analogs include potential mutagenic and carcinogenic effects, possible effects on tissues with high mitochondrial content (hepatic and cardiac tissue) and possible effects on the reproductive system. From a phase II study on ZDV/3TC no major toxic side effects were reported in the newborn. Transient elevations in liver enzymes were reported
from the phase II study and the PETRA study. Long-term follow up is required to ascertain long term
risks of exposure to 3TC.

Immunotherapy and antiretroviral regimens

The ACT 185 phase III study is underway in the USA. ZDV with HIVIG/IVIG is given in the
prepartum period followed by ZDV alone in the intrapartum period, with the combination given
postpartum to the child.

Phase I trials looking at a combination of ZDV with either monoclonal neutralizing Ab (to
child) or the Genetech/Biocine gp120 vaccine (to child) or the canarypox gp 160 9 to child) or Genetech
Ggp l20 (prepartum) are either planned or underway in the USA.

Resistance and the use of antiretrovirals in pregnancy

Women who have received extensive prior ZDV therapy may be infected with viral strains that
have reduced susceptibility to ZDV. These resistant strains may be transmitted from mother to fetus but
the frequency with which such transmission occurs is unknown. Resistant virus appears to emerge more
quickly in advanced stage of disease. In one study after 12 months of therapy, viral isolates from 89% of
patients with late stage disease and 31% from early stage disease were resistant (13). However, isolates
from only 33% of late stage patients demonstrated high level resistance. In patients with early stage
disease, high level resistance appeared to be delayed until after 24 months of therapy. Therefore ZDV
resistant strains are likely to be more common in women with advanced stage disease, receiving prolonged
therapy.

The capability of ZDV to reduce HIV transmission may be decreased for mothers in whom ZDV
resistant strains predominate but this assumption is not yet supported by data. In the developing world few
women will have had prior access to antiretroviral therapy before falling pregnant, therefore resistance
may be less of a problem than that seen in the USA or Europe.

Concerns about the potential long-term adverse effects among women include the development of
ZDV-resistant virus when ZDV therapy is used intermittently to reduce perinatal transmission, especially
if used for more than one pregnancy, and the potential effect such resistance could have on disease
progression. Although the results of some studies have demonstrated an association between emergence of
ZDV resistance and total duration of ZDV exposure, none of the study designs have specifically addressed
the effect of intermittent therapy on the development of resistance (14).

Acceptance, implementation and adherence

Acceptance of these regimens in the developing world needs to be studied further. In some places,
for example Kigali, most clinic attenders were willing to find out their HIV status; two-thirds of women
tested in 1992/93 returned for post-test counselling. At Baragwanath Hospital, Soweto, South Africa,
96% of women attending antenatal clinics consent to testing and return for further care (personal
communication from Dr McIntyre). The reason for the high uptake of testing may be because women in
Soweto do not perceive themselves to be at risk. This is in contrast to findings in Cote d'Ivoire and in
Kenya where although antenatal attenders consented to testing, a substantial proportion of women did not
return for their results or for post-test counselling. Failure to return for results may be due to inadequate
care, counselling and support during and after pregnancy for women testing positive, or to the fact that
although the women consented to testing, they did not wish to know their status because of their perceived
higher risk of transmission.
Implementation of a regimen in poorly resourced, overburdened midwifery/obstetrical units will depend on the number of women consenting to testing and returning for their results, on the simplicity of the regimen (oral dosing, absence of an intrapartum arm and minimal management in labour) and the ease with which they can return for follow-up. Adherence will depend on how easy the regimen is, for example, single agent vs multiple agents, oral dosing, bd dosing vs multiple doses during the day, if they have to be taken with/without food and if there are minimum side-effects. It is clearly very important that the health worker and the client understand the regimen and its benefits.

Questions have been raised regarding the ethics of stopping antiretrovirals after delivery. The reason for using antiretrovirals in pregnancy is to reduce MCT and the beneficial effect it can have on the mother's health is secondary. In settings where access to antiretrovirals is not the norm, the cost of continuing these drugs for the duration of the mother's life will be prohibitive. None the less, governments, health ministries, pharmaceutical companies and international agencies should continue to endeavour to make these drugs increasingly available to people in areas where the majority of HIV-1 infection occurs. At the same time, research should continue with other compounds (e.g. Pokeweed antiviral protein, immune-boosting drugs like escador) which may be effective antiretrovirals for the prevention of MCT.

Antenatal care and the use of ARV in pregnancy

Antenatal care is almost universal in the developed world whereas in the developing world it varies from just under 90% in Southern Africa (excluding Mozambique) to 66% and 60% in Eastern and Western Africa respectively. Furthermore, in these areas (Eastern and Western Africa), fewer than 40% of deliveries are assisted by a trained attendant and only 30% of deliveries take place in health institutions (15). By contrast, 76% of women in Southern Africa deliver in an institution and 79% have a skilled attendant at delivery. The purpose of antenatal care is to prevent common complications (anemia, tetanus etc) to detect pregnancy complications early and to provide health education. It also represents an opportunity to treat existing diseases which may be aggravated by pregnancy (e.g. malaria, tuberculosis) or which may have a negative impact on outcome for mother and infant (e.g. STDs).

Identification of HIV-infected women during pregnancy allows for several beneficial interventions, including the possible introduction of strategies to reduce transmission. In addition, with appropriate pre- and post-test counselling, women can make informed decisions about their present pregnancies (which may include termination), feeding options for their babies, and for their own future reproductive health. If few women are accessing antenatal care and even fewer accessing intrapartum care one needs first to improve access to care before implementing interventions. If few women have access to care in the intrapartum period, regimens need to be adapted so that an intrapartum intervention is not required. If few women have access to antenatal care but deliver in a midwifery/obstetrical unit, then an intervention should be looked at that only requires intrapartum management or treatment.

If an antenatal clinic is going to offer HIV-1 testing, the testing should be done with proper pre-test counselling and informed consent. The test should be voluntary and post-test counselling should be available to every woman consenting to be tested. Women testing HIV-negative should receive information regarding their status and how to remain negative, and counselling in the antenatal setting should be used as a preventive strategy. Women testing positive should continue to receive counselling as part of antenatal care. Issues regarding disclosure need to be addressed as ongoing counselling continues in the antenatal set-up.

The cost of possible interventions should include the cost of HIV testing as well as the cost of training and supporting counsellors. Future research should be directed towards making HIV testing
more affordable and accessible to all pregnant women, for example salivary HIV testing or other testing techniques that do not require sophisticated laboratories or trained laboratory technicians, that can be done by primary health care workers (with pre-test counselling and informed consent) and that are sensitive, specific and cheap.

In overburdened health facilities it is difficult to maintain a high standard of counselling. Nurses in these settings are usually trained as counsellors and in busy antenatal clinics where the nurse has to perform many functions, adequate counselling may not occur. Innovative models of counselling need to be developed to overcome these difficulties as well as using more appropriate human resources to do the counselling (peer counsellors, NGOs etc). In the Gauteng Province in South Africa, the health department is training lay counsellors for this purpose.

Delivery care and prevention of MCT

It is difficult to envisage the provision of antiretroviral therapy in resource-poor settings where even gloves, clean needles, disinfectant solutions and intravenous infusion sets may not always be available. Health officials should see the introduction of universal precautions in medical settings as the first priority before considering spending money on antiretrovirals.

Obstetrical procedures that may increase MCT should be modified. This may include reducing the number of episiotomies, reducing the rate of artificial rupturing of membranes thereby preventing prolonged rupture of membranes, minimizing the use of vacuum extraction and assisted deliveries that may damage the skin of the neonate. Decreasing the duration of labour and possibly the second stage of labour, may also help to reduce MCT. The use of vaginal lavage with chlorhexidine may be beneficial in the prevention of MCT in women whose membranes have been ruptured for more than four hours. Caesarian section in some settings has been associated with decreased transmission, but would not necessarily be an appropriate intervention in poor resourced delivery settings. Wiping bloody secretions off the neonate may decrease exposure to infected body fluids. Minimizing vigorous nasogastric suctioning that damages oral mucosa may also decrease transmission through breastfeeding.

Information regarding transmission through breastfeeding should be given to the HIV-infected mother in order to ensure that she makes an informed decision regarding feeding. Post-natal care for the mother and infant should be provided. Recommendations regarding the use of PCP prophylaxis in infants born to HIV-infected women should be followed. The mother should have access to safe contraceptive methods should she wish not to fall pregnant. Advice about how to reduce the risk of transmission through breastfeeding with bleeding and cracked nipples should be given. The mother should also be shown how to inspect the mouth of her infant for oral thrush and breakages in oral mucosa to minimize the risk of transmission through breastfeeding. In some settings, such as Thailand, Soweto, South Africa, and parts of Brazil, subsidizing of formula feeding may be considered.

Minimum requirements for implementation of regimens

- Access and use of appropriate antenatal, intrapartum and postpartum care with adequately trained health workers
- Adequate pre- and post-test counselling services
- Affordability of reliable HIV testing
- Laboratory facilities to monitor blood parameters - a hemoglobin may be all that is necessary
- Delivery units with access to disinfectants, gloves and needles
- Acceptance and uptake by HIV-infected women
• Regimen that is easy to implement:
  i) may not require testing/counselling e.g. vaginal disinfectant, vitamin A therapy
  ii) oral medication, daily or bd dosing
  iii) no need for intrapartum dosing
  iv) no need for postpartum dosing
  v) able to store at room temperature

• Regimen that is cheap (cents not dollars)

Priorities for future research

• Further research into vaginal disinfectant
• Research into modification of breastfeeding practices in an attempt to reduce post-natal transmission e.g. early weaning, withholding colostrum, pasteurization of breastmilk
• Research into alternatives to antiretrovirals e.g. small molecular compounds (Pokeweed antiviral protein) and immune boosting drugs
• Research into vaccine development for subtypes infecting the majority of the global population
• Research into effective and safe contraception to prevent pregnancy in HIV-infected women
• Research into oral abortion drugs to ensure safe termination of pregnancy if so desired by HIV-infected women
• Research into the development of more effective and acceptable microbicides that prevent HIV infection in women.

Conclusions

Results from studies designed to prevent MCT of HIV-1 will suggest different strategies. The completion of trials with antiretroviral agents, possibly in combination with hyperimmune immunoglobulin, vitamin A, caesarian sections, or vaginal lavage will not only help to understand the efficacy of the intervention but will also provide insight into the timing and the risk factors involved in transmission.

Short course antiretroviral therapy and less costly drug regimens, if effective, should be implemented for use in developing countries. Results, when available, from studies looking at the role of antiretrovirals in the intrapartum period should be analysed in an attempt to make regimens like this available in the developing world where few women have antenatal care. In areas where women access antenatal care but deliver elsewhere, antepartum interventions may be more applicable.

Post-natal transmission may be minimized by the use of antiretrovirals in this period for the mother and the infant. Further investigation is also needed into combination therapy and the new classes of more potent antiretrovirals e.g. protease inhibitors and the newer non-nucleoside reverse transcriptase inhibitors and their role in preventing MCT of HIV-1.

The ACTG076 study showed that an antiretroviral drug could significantly reduce MCT. The mechanism of protection may be due to reduction of maternal viral load and/or an inhibition of viral replication in the fetus. The challenge now facing researchers and public health specialists is to find an antiretroviral regimen that is not only effective, but short, simple and affordable for global use. The mechanisms for implementing interventions should be easy so as not to stress the already overburdened health systems in developing countries.
Table 1: Antiretroviral regimens in various studies

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<td>ZDV 500 mg then 250 mg bd</td>
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<td>ZDV &amp; 3TC to mother &amp; child X 7 days vs placebo</td>
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References


Implications of Antiretroviral Therapy for Voluntary Counselling and Testing

Rossana Ditangco*

Voluntary counselling and testing (VCT) are important components of HIV/AIDS prevention and care. They encourage and facilitate preventive behaviour and early access to care (1). However, the setting up and running of such services in resource constrained settings can be difficult. VCT services require trained staff to provide medical and psychosocial support, and quite a sophisticated infrastructure including facilities with well functioning referral procedures.

The problems are further complicated by the development of new antiretroviral (ARV) treatments. ARV treatments could in theory make HIV infection a chronic illness and prolong life beyond what is now the norm. There would therefore be a new rationale for requesting HIV testing which could lead to increased demand for voluntary testing, and consequently for HIV/AIDS counselling services.

Will ARVs influence the demand for voluntary counselling and testing?

From 1985-1990, most of the HIV tests done in the Philippines were for serosurveys of risk groups in an attempt to estimate the extent of the infection in the country (2). By 1993, over 1.2 million HIV tests were carried out, half of which were on overseas contract workers who have to present proof of HIV-negative status to host countries, over a third on blood donors and around one fifth on female commercial sex workers as required by the Sanitation Code. A small fraction of the tests were done on members of the general population seeking voluntary counselling for risk assessment. Although a nationwide survey in the late 1980s showed a high level of AIDS awareness, only 21% to 30% perceived themselves to be at risk for HIV infection (3). A review team in 1994 commented that the public has limited access to HIV testing, must pay for all the tests, is unaware of cheaper facilities at government agencies and may be unable to afford private doctors (4).

At the Remedios AIDS foundation, a pioneer AIDS organization with extensive services that include outreach, training, networking, counselling (face-to-face and telephone hotlines) and HIV testing, the number of consultations peaked in 1992-1995. This was attributed to a massive media campaign during that time with strong support from the Department of Health (DOH) and funding agencies (5). A decline in the number of consultations was observed in 1996. This was in turn attributed to the lack of information campaigns and IEC materials due to the shift in priorities and concerns of the DOH, lack of funds and changes in hotline telephone numbers.

Questions most commonly asked by members of the public were on modes of transmission and prevention of HIV infection. Inquiries about treatment were rarely encountered even after the Vancouver conference which shows that the general public is largely unaware of the new developments. This is probably due to the fact that there has been little coverage of these issues in the media which is the most common source of information for the general public (6). The executive director of Reach Out AIDS Education Foundation believes that there is no relation between knowledge about ARVs and the demand for HIV testing; perceived risk influences decisions to undergo counselling and testing (7).

Even in well resourced countries, people test late in the course of HIV infection. In a review of HIV testing patterns of people diagnosed with AIDS in the USA between June 1990 and December 1992, it was noted that 36% were tested within 2 months and 51% within one year of AIDS diagnosis.

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Individuals primarily sought testing because of illness (58%), belonging to a known risk group (13%) and having an HIV infected partner (8%) (8).

It is not clear how developments in ARV treatments will influence HIV testing patterns. The following are probable reasons why HIV health seeking behavior will not improve in spite of the development of effective drugs:

1. People who know they may be infected are often unwilling to seek services of any sort including testing, for fear of disapproval and discrimination. This is because the behaviours that lead to HIV infection frequently provoke negative social and moral judgments (9).

2. Long clinical latency - health seeking activity is usually triggered by the presence of signs and symptoms. Therefore, an infected individual who is unaware of his/her HIV status will not usually seek medical care. This happens even in well resourced countries.

3. Perceptions of risk - data in the Philippines shows that the level of HIV/AIDS awareness does not correlate with perceived risk for the infection.

On the other hand, it is also possible that public knowledge about the developments in ARV treatments will increase and positively influence the demand for voluntary counselling and testing. Reasons for this include:

1. More aggressive campaigns to promote voluntary counselling and testing using ARVs as the rationale.

2. Developments in ARVs will somehow influence perceptions of risk.

3. Individuals who believe they have been exposed to HIV infection may seek early ARV treatment to arrest infection.

4. To prevent infecting partner(s).

**Could the present infrastructure cope with an increase in demand for voluntary counselling and testing?**

The number of existing health care facilities in relation to current disease prevalence is a good predictor of coping capacity. Even in well resourced countries like the UK, there is now concern about the capacity of current infrastructure to cope with increasing demand for voluntary counselling and testing as a result of developments in ARVs (10). These new demands will be an additional burden in settings where services are saturated or overwhelmed by the burden of HIV/AIDS.

Although the prevalence of HIV infection and AIDS in the Philippines remains low as compared to neighbouring countries in Southeast and South Asia, the potential for rapid spread of the epidemic is recognized. The number of HIV positive individuals as reported by the Philippine DOH could be underreported by a factor anywhere from 3 to 1,000 according to WHO and various other estimates (3). A steady rise in the number of new cases diagnosed each year is being observed. It is projected that by the year 2000, the cumulative total of HIV infections will be 90 000 while that for AIDS will be 15 000.

Voluntary counselling and testing services for persons perceived to be at risk for HIV infection (either by the person himself or by others) are offered in 100 private STD clinics (11), 143 social hygiene clinics, antenatal clinics, selected hospitals, narcotics treatment centres and offices of NGOs
working in AIDS. As of 1995, 45 laboratories in regional hospitals and medical centres were performing HIV screening tests (12). This is supplemented by over a hundred accredited private laboratories in the country.

Requirements for accreditation include a supervising pathologist and a licensed medical technologist who has undergone training and has passed the proficiency exam on HIV testing, regularly conducted by the Bureau of Research and Laboratory (BRL) and the Research Institute for Tropical Medicine (RITM). With the continuous training being conducted by the National AIDS/STD Prevention and Control Programme (NASCP) of the DOH, for front-line and hospital-based health workers, the Philippines seems to be prepared, in terms of manpower, to cope with the potential increased demand for voluntary counselling and testing.

Cost is as ever a major obstacle. Even HIV tests may be unaffordable for most of the population in need - in private laboratories, an HIV screening test costs between Ph 100 to Ph 600 (approx. US$ 4 to US$ 24). At present, government centres offer testing services at a very affordable price, if not for free, but there are frequent problems with availability of laboratory supplies and reagents.

**Developments in ARVs will influence the content of counselling**

The introduction of ARV treatments has raised new and difficult issues for counselling. These include the psychosocial stress created by knowing that effective drugs exist but are unobtainable. The other major new issue in counselling is adherence. This is a crucial factor contributing to treatment effectiveness; counsellors have a major role to play in supporting and facilitating adherence.

Ninety two percent of the world’s HIV infected people have no access to, or cannot afford the basic treatments for HIV/AIDS (13). The majority live in poor countries. Even in well resourced Western countries, drug accessibility is also a problem in deprived and underserved communities. More and more people living with HIV/AIDS (PLHA), even in resource poor countries are becoming aware of new developments in ARV treatments and are desperate to obtain the drugs.

In the Philippines, the Department of Health has recorded a cumulative total of 878 HIV-positive people (as of February 1997) since the first reported AIDS case in 1984. Of these, 155 have died. Although the government believes that a preventive approach to HIV/AIDS is still most cost-effective in the absence of an effective cure and vaccine, reduction of disease impact on the individual and the community is one of the main objectives of the National Medium Term Plan for the Prevention and Control of HIV/AIDS in the Philippines (14). This includes clinical management and support for people living with HIV/AIDS.

By 1994, Zidovudine (AZT) was made available through government subsidy at the two referral centres San Lazaro Hospital and the Research Institute for Tropical Medicine (RITM), that provide clinical care for HIV/AIDS patients. AZT and Zalcitabine in combination soon followed. At present two protease inhibitors have been approved for compassionate use while another is awaiting approval from BFAD pending the completion of local clinical trials. At RITM, the direct cost of the infection per person per year (excluding antiretroviral drugs) ranges from Ph 6000 to 144,000 (approx. 240 to US$ 6000) depending on the clinical stage of the disease (15). Since it started providing clinical care for HIV/AIDS patients, there have been 152 cumulative cases. Of these, 59 have died, 60 are asymptomatic and 33 are symptomatic (16). Last year the government subsidy for medicines (antiretrovirals and drugs for opportunistic infections) was more than Ph 600,000 (US$ 24,000). San Lazaro Hospital received Ph 1.8 M (US$ 72,000) from the national budget for medicines. At present there are about 80 patients who regularly visit the outpatient clinic and there is about one new case per week (17).
The content of counselling for people with HIV/AIDS should now take into account issues arising from drug inaccessibility. It has been suggested that ARVs should not be discussed in settings where drugs are not available (1). With the rapid dissemination of information regarding ARVs, discussions about ARVs are initiated by the PLHA themselves and counsellors can no longer avoid the issue. Where the treatments are available, counselling in relation to ARV treatments should now include provision of information about accessibility of drugs, their advantages and limitations, currently available data on efficacy, side effects and compliance. In situations where the new treatments are not available, counsellors will need considerable skills and sensitivity to support those wishing to obtain the drugs but having no means of doing so.

Counselling is important to ensure adherence

Problems concerning ARVs do not end once these drugs become accessible. Failure to adhere to prescribed medications may lead to viral resistance and treatment failure. Combination therapy is very expensive and poor adherence means a waste of valuable resources. The counselling process should be able to address the factors that adversely affect adherence.

Combination therapy is complicated. ARVs have to be taken many times a day, some even six times a day. Some must be taken on an empty stomach, others with meals, while others require high fluid intakes. Some have unpleasant side effects which may become intolerable, but which otherwise must just be accepted. ARVs mean additional medications for PLHA who are already on a multiple drug regimen for prophylaxis and treatment of other HIV-related conditions.

Other factors that could adversely affect adherence include the psychological state of the infected individual (such as anxiety or depression) and the lack of support and encouragement from immediate family. Counsellors must address these issues in order to ensure maximum adherence to the treatments.

What are the minimum requirements for counselling and testing in relation to ARV treatments?

To cope with the new demands for voluntary counselling and testing the following minimum requirements must be met:

1. Availability of facilities that could provide HIV tests at an affordable cost. Cost effective strategies on HIV testing should be developed in order to maximize limited resources and bring down the cost of HIV testing. It is possible that information about developments in ARVs will encourage even the so-called “low risk” groups to undergo testing. It is therefore important that during pre-test counselling, health care providers be able to identify individuals who appear to be at high risk and those who appear to be at very low risk of HIV infection. In this way, unnecessary tests will be minimized and resources will not be wasted. In some countries like the Philippines, serum pooling is a cost effective strategy for HIV testing.

2. Health care workers who are competently trained to provide information and counselling, including dealing with the stress associated with drug inaccessibility, and problems with adherence.

Appropriate training for health care providers is very important. There should be continuous training in order to increase the number of health care providers in the field equipped to deal with HIV/AIDS. Health care workers should also be well informed regarding recent advances in therapies for HIV infection.

The Philippine Department of Health, through its various agencies, conducts regular training in order to expand the capabilities of government centres on HIV/AIDS management. This is in
anticipation of the projected increase in the HIV/AIDS incidence in the country. BRL and RITM (described on page 3) regularly conduct proficiency training on HIV testing for medical technologists from government and private laboratories. RITM, through the Japanese International Cooperation Agency, conducts the “In-country Training Programme on the Diagnosis and Management of HIV/AIDS and other STDs in the Philippines” every year. Participants are the hospital based HIV/AIDS Core Team composed of doctors, nurses, medical technologists and social workers and a partner NGO. There are also training programmes for front line health workers spearheaded by the AIDS Unity of the NASPCP, sometimes in collaboration with NGOs.

At present, the content of HIV counselling is standardized and includes basic information about HIV/AIDS, the modes of transmission, risks of infection, the meaning of the HIV test and its result, risk assessment, risk reduction and possible impact of the infection on the individual. Post-test counselling when the result is positive includes providing initial emotional support, risk reduction information and referral for further management and support (18). Discussion about antiretroviral therapy is not usually introduced at this point unless a client inquires about it and in this case, referral to RITM or San Lazaro is recommended. If the test result is negative, post test counselling should provide or reinforce prevention education.

There is a need to regularly update the content of these training programmes to cope with the rapid changes in HIV therapy and to inform health care practitioners and educators about the implications of these new therapies.

Women and HIV

In the Philippines the male to female ratio of HIV infection is 1.3 to 1. The majority of women are between 20 - 29 years old and the majority of men are between 30 - 39 years old (19). The majority of female adult patients seen at RITM are working in the “entertainment” sector. (Women working in this sector are in fact obliged to have sex with clients.) The next largest group consists of women whose partners are HIV infected.

Reproductive health services are available in antenatal clinics of government health units, social hygiene clinics, private STD clinics, other medical centres both government and private, and NGO offices. Social hygiene clinics almost exclusively cater for women engaged in commercial sex and working in “entertainment”. In the Philippines, there is a real need for a separate system to address women’s issues and provide specific services. Data collected from the Remedios AIDS hotline showed that almost 95% of its callers are males. With the establishment of the Women’s AIDS Hotline and the availability of female counsellors 8 hours a day, female callers rose from 5% to 15% to 20% (5).

Mr Jomar Peralta of Reach Out believes that although women’s issues are unique, it may not be cost effective to establish separate services as demand is still low - there is a plethora of advocacy activities and educational information for women. There are however several NGOs in the country whose programmes centre on women (5). In addition, the Department of Health has launched the Safe Motherhood and Women’s Health Project supported by five donor agencies.

One of the strategies of the NASPCP is that women attending antenatal clinics will receive health education. Women attending antenatal clinics who are found to be HIV-positive will be counselled for contraception. Pregnant women found to be HIV infected will be given priority for AZT treatment.

Early cases of documented HIV infection during pregnancy were on female prostitutes in 1990. Since 1984, there have been eleven documented cases of perinatal HIV infection. At the moment two HIV infected pregnant women in San Lazaro Hospital and one in Ospital ng Maynila are receiving
antiretroviral treatment. They have regular prenatal care and preparations are already being made for their deliveries. NGOs are actively participating in providing the necessary support for these pregnant women. Although not explicitly stated in the NAPSCP strategy, postnatally, these women will be grouped with those HIV infected patients who will receive optimum clinical care including access to antiretroviral drugs. They will be advised about the risks of transmission through breastfeeding and helped to make informed decisions about how they wish to feed their babies.

At present, pregnant women with HIV are being cared for in two centres in Metro Manila. The Department of Health has made clear statements about management of HIV infected women and current guidelines on treatment are being adapted. Similar to the general belief regarding the true burden of HIV infection in the general population, current prevalence data on HIV in pregnancy may represent the tip of the iceberg. With the lack of a strong campaign on women’s issues, women may not be aware of the risks of infection nor of services available.

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Ethical Challenges Posed By New Advances
in the Antiretroviral Treatment of HIV Disease

Ronald Bayer*

Introduction

The advances in the treatment of HIV made during the past two years, marked by the use of combination therapies relying on two nucleoside analogues and a protease inhibitor, have been greeted with enormous enthusiasm. Although some have remained skeptical, recalling the excitement that surrounded monotherapy with AZT a decade ago and the mistaken assumption that CD4 counts could provide a reliable surrogate marker for disease progression, it is clear that for many clinicians and tens of thousands of their patients, a new era of AIDS treatment has begun. However today's hopes will be viewed from the vantage point of the next years. This new sense of therapeutic efficacy has produced ethical challenges that require immediate attention. Some may only require attention if the new regimens prove to be as effective as their most enthusiastic proponents suggest.

In nations where the cost of these new drug regimens does not place them beyond reach, it will be necessary to confront questions of equity. Who will have access? Who will decide? Must all who can benefit from the new treatments have access regardless of their ability to pay? If the social cost of universal access is deemed prohibitive, would equity require that none have access to the new therapies? Do those who provide care to patients with HIV have special claims to the new combination therapies - for post-exposure prophylaxis if not for treatment? Do the prospects of prophylaxis during pregnancy establish special claims and priorities?

Many clinicians refuse to prescribe the new combination therapies—even when cost is not an issue—because of concerns about the ability of certain patients to remain adherent. Can such refusals be justified on paternalistic grounds? In the patient's best interest? Can they be justified on public health grounds—to prevent the development and spread of drug resistant strains of HIV?

A second broad set of questions that may be posed centers on the balance between coercion and voluntarism in the structure of AIDS policy. Do the benefits of the new combination therapies warrant a reconsideration of the balance that has been struck over the past decade and a half? Do they warrant a shift toward a tuberculosis control model? In short, when can the prevention of HIV justify the abrogation of the right of privacy and autonomy?

Finally, the clinical achievements marked by the new combination therapies underscore the impact of the global distribution of medical resources, thus posing the question of what those in the industrialized world owe those in the developing nations where upwards of 90 percent of HIV infections occur. Can principles of justice be brought to bear under these circumstances?

It would be impossible to consider all of these questions in the space available to me for this consultation. Indeed, a full consideration of these ethical challenges would constitute a volume on the ethics of AIDS in the last years of the 20th century. What I can hope to do is to lay out schematically the issues that have emerged, posing "solutions" only where space and my own limited knowledge permit.

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Justice and/or access to the new combination therapies

At its most fundamental level the principle of justice requires that within a given society no individual be deprived of access to effective medical treatment because of inability to pay for such services. It also requires that patient costs associated with care should not represent an undue burden. Beyond that basic principle there is considerable dispute among those concerned with the ethics of health care, and the disputes have direct relevance to issues at hand. Must people be guaranteed access to all effective AIDS therapies regardless of cost? Can societies assure access to a basic level of AIDS care but not to the new therapies, however effective? If a society does not guarantee access to all AIDS therapies, should people be permitted to secure care by paying for it themselves? Will the option of permitting individuals to purchase care not generally available produce a multi-tiered health care system in the case of AIDS that is inequitable? How do constraints on resources available to the health system shape responses to these questions?

The answers to these questions depend, in part, upon the extent to which societies commit resources to the health care sector as compared to other social needs; the extent to which resources in the health sector are devoted to curative, as compared to preventive, medicine. To claim that a single right answer can be given to the most basic questions posed above would be to ignore the socio-political contexts within which health care decisions must be made.

But with these caveats in mind it is clear that no policy that subjects AIDS care to invidious discrimination can be justified on ethical terms. Thus, for example, if a society is willing to pay for dialysis, the cost of which is greater than the cost of the new combination therapies, it would be inequitable to establish a limit on the cost of AIDS care that is lower than that associated with end-stage kidney disease. The assumption should be that medical interventions that produce equivalent improvements in quality-adjusted life years at equivalent costs should be treated equally. That is, however, but a starting point. In the absence of such invidious discrimination, a system may still violate the basic norms of justice noted at the outset of this discussion.

In the United States--the case I know best--the current pattern of access to the new combination therapies is characterized by profound inequities, given the resources available and the pattern of health care expenditures. But these inequities are embedded in a health care system that is characterized by inequities, where ability to pay shapes access to care. Thus, while those who are covered by the federal/state Medicaid program for the poor have access to the new combination therapies, others with limited resources do not. Indeed, some state programs designed to assure access of medically uninsured people with HIV/AIDS to therapeutic agents (the ADAP program) have explicitly decided to exclude all the protease inhibitors because of cost. Others have established arbitrary limits on the number of persons who will have access to the protease inhibitors and will use a lottery system to establish the cohort. Finally, some private health plans have established limits on the annual pharmacy coverage for all diseases, and these limits fall short of the cost of the new combination therapies.

It is crucial at this juncture to make a brief observation on the question of the price of ARVs. By and large, those concerned with medical ethics have ignored or avoided the issue of the fairness of prices of vital therapeutic agents. This is, I believe, a profound error. To focus solely on the question of distributive justice, without addressing the fairness of prices, is to hold patients, their families and governments hostage to the dictates of the pharmaceutical industry. This is not the place to resolve the question of whether the extraordinarily high price for ARVs, and especially the protease inhibitors, is in fact fair. But it is appropriate to argue that the market price of a drug is not necessarily a fair price. In the case of desperately needed life-extending, life-enhancing drugs for those suffering from HIV/AIDS, markets alone are not the appropriate mechanism for making appropriate price determinations. Human needs ought to play a central role in determining the price of ARVs. Thus prices must be viewed as the legitimate focus of political discussion, broadly understood.
How to balance a fair return on investment, how to encourage continued investment in research where there are many false starts, while recognizing the needs of the desperately ill, should become the subject of vigorous debate. It should emerge as a central issue on the agenda of those concerned with the ethics of the AIDS pandemic, which increasingly affects the lives of men, women, and children in poor and resource-constrained nations.

By way of summary, in relatively wealthy, advanced industrial nations the principle of justice in health care dictates that all individuals who could benefit from the new combination therapies should have access to them regardless of ability to pay. In nations where resources are constrained and where a commitment to providing combination therapies to all who could benefit would have a negative impact on other life-extending/life-enhancing medical interventions or on other critical social expenditures, a careful cost/benefit analysis will be essential to ensure that those with AIDS and HIV are not subject to invidious discrimination.

**Restricted access to ARVs under circumstances of scarcity**

When it is impossible to provide ARVs to individuals who might clinically benefit, because of severe economic constraints for example, it might nevertheless be ethically defensible to provide access to selected classes of persons. The issue here is the classic circumstance of rationing and whether allocations to some, but not all, can be morally justified. I have already addressed the question of allocating ARVs to the population as a whole. I now want to take up the question of whether health care workers should be provided with post-exposure prophylaxis with ARVs that are not available to the patients for whom they are providing care. Would such provision to those who are already relatively privileged be unacceptable and thus a violation of the principle of equity?

A case could be made for such provision on grounds of utility and reciprocity. The argument would take the following form: health care workers are needed to take care of hospitalized patients with HIV disease. In the course of their work they may be exposed to HIV and, as a consequence, may become infected and develop disease, thereby reducing the pool of workers capable of caring for patients with HIV disease. Viewed from this perspective, society in general and patients with HIV in particular might have an interest in restricted provision to this group. 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 such provision. Finally, it could be claimed that society owes a special responsibility to those who take on even the limited risks associated with caring for those with HIV infection.

But what is troubling about both these claims is that they prove too much. The arguments could be extended to a claim not only for prophylaxis but for ongoing treatment were prophylaxis to fail. Hence a case would have been made for a special class of individuals in terms of ongoing care. It would, of course, be possible to restrict the claim to the relatively brief period required for prophylaxis, but that would imply interrupting potentially effective, life-prolonging treatment that had already begun. Prophylaxis offered to health workers in post-exposure circumstances would only be morally justifiable if such interruption of treatment were envisaged. Failure to limit therapy to purposes of prophylaxis would create a privileged class with access to treatment. It would mean that health workers infected nosocomially would have privileged access in relation to those infected sexually or by any other means.

A final observation regarding restricted access to the new combination therapies for purposes of prophylaxis can now be made with regard to pregnant women. Under conditions of scarcity, where combination therapies are not available to patients in general, nor to women who are not pregnant, would it be ethical to provide therapy for purposes of reducing the risk of vertical HIV transmission? The answer to this question is no different from that which would be given to the question of special access to monotherapy with AZT during pregnancy for purposes of preventing vertical transmission. It
does not represent a violation of the rights of pregnant women, nor an unjust distribution of resources to offer pregnant women preventive therapy. A nation too poor to afford therapy for all who could benefit might be able to afford the much more limited expenditure of resources that would be entailed in providing ARVs to prevent MCT. This would be especially true if the preventive course were administered during the very last stages of pregnancy and shortly after the birth of the child.

While it might be considered cruel to end such therapy after delivery, that would simply return the formerly pregnant woman to the same status as her equally situated compatriots. It does not treat a woman "merely as a vessel" to offer her the opportunity to save the life of her child when resources might not permit the provision of life-extending therapy to her. She might, of course, decline such prophylaxis. Many would not.

Restricting access to combination therapies: paternalism, public health and the problem of resistance

Where resource constraints do not provide a barrier to care, it may nevertheless be necessary to consider the question of whether some patients should be denied access to the new combination therapies for clinical or public health reasons. This issue has been the subject of intense discussion in the United States, but it is relevant to other countries where resource constraints do not render such consideration beside the point.

Given the difficulties of securing complete adherence to any drug regimen, the challenges involved in combination therapy for HIV disease are daunting. The prospect of resistance not only makes individual patients more vulnerable, it also raises the spectre of a public health threat that could well neutralize recent therapeutic advances. Clinicians have been concerned about how to communicate the extraordinary importance of strict adherence to their patients. Patient-oriented newsletters and magazines have warned against taking "drug holidays."

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 to previous treatment demands or on predictions about future behavior based on defined patient characteristics? Are there entire classes of individuals, i.e., the homeless, those suffering from certain types of mental illness, or injecting drug users, to whom the drugs ought not be offered?

The threat of resistance has put the question of adherence at the center of discussions of the treatment of tuberculosis for more than four decades. With the upsurge in tuberculosis in the late 1980s and the increasing incidence of multi-drug resistant tuberculosis, directly observed treatment (DOT) emerged as the standard of care. But DOT regimens for TB involve taking drugs at most once a day and often only two or three times per week. The sheer logistics of combination therapies, which require medication several times a day, preclude DOT as a useful approach.

Were the problem exclusively one of individual patient welfare the question would be whether predictions regarding the probable inability of a patient to adhere to treatment could justify denying access to a life enhancing and extending therapy. Here the claim would be that the patient her/himself would be better off in the long run not having access to drugs because it would protect against the development of resistance and allow benefit from combination therapies in the future. It would be very difficult to justify such denial on paternalistic grounds in the face of expressed patient preference for treatment except in the presence of overwhelming evidence that a patient could not or would not be adherent. Where such evidence exists, a decision to limit access to care could be ethically justifiable.
But 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. Only an individualized determination that a given patient will not be adherent and that he or she is likely to engage in behavior that could transmit resistant strains of HIV could justify the withholding of protease inhibitors.

Patient autonomy should, as a matter of principle, be the guiding norm in clinical determinations. But autonomy is not absolute and may be overridden when the well being of the community is at stake. Typically this occurs in the context of infectious diseases such as TB, where patients may be compelled to undergo testing and treatment. The interests of the public health and the patient are thus served. What makes the current situation so difficult and troubling is that the interest of the public may be in conflict with the preference of the patient for therapy.

Denials of access to therapy should never be based upon broad social characteristics such as mental illness, homelessness or drug use, although such conditions might well increase the index of suspicion and trigger a careful individualized assessment of the person’s prospects for adherence. Patients must be apprised of the rationale for withholding therapy, and such decisions must be reviewed periodically, as changed patient behavior could affect the clinical determination. Decisions to limit access to therapies because of concerns about adherence must not become a pretext for rationing, cloaking denials based on economic considerations.

To the extent that deprivations 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 access to life-extending therapies when remediable social conditions contribute to their inability to adhere to therapies.

The new combination therapies and the future of voluntarism in AIDS policy

AIDS prevention policies took shape in the early 1980s, during a period of therapeutic and pharmacological impotence. In that context it was clear that the strategy of prevention had to focus on creating the context within which mass behavioral change could occur and be sustained. A broad consensus developed that the strategy had to be centered on the protection of the rights of people with or at risk for HIV. Recourse to the compulsory traditions of public health--those, for example, that inform tuberculosis control programs, and vaccine efforts--was rejected. Not only would important human rights be violated, but such an approach to HIV prevention would, it was argued, be counterproductive, "driving the epidemic underground."

As the prospects for therapeutic intervention improved in the late 1980s a number of public health officials, especially in the US, began to argue that it was time to reconsider the ethics of AIDS prevention efforts and to draw upon the experience and lessons of traditional public health practice. For example, there was a renewed interest in partner notification. Most important, increasing numbers of clinicians and public health officials began to question the appropriateness of the exacting requirements of specific informed consent for HIV testing. Some suggested that the "normalization" of AIDS required the routinization of HIV testing under conditions of presumed consent--the standard that governed most other blood tests in clinical settings.

It is inevitable that the progress represented by the new combination therapies will foster further discussion in this regard. Most relevant are the findings that viral load may be reduced to technically undetectable levels. What are the implications of these findings for HIV testing? Were it possible to render HIV infected individuals non-infectious, would mandatory testing be justified? This is a question
that presumes much more than the scientific data warrants. But were that achievement possible, and were a practical, monitorable therapeutic regimen achievable without gross intrusions on privacy and liberty, the public health norms that govern vaccine programs might be applicable if the protections of the social rights of people living with HIV/AIDS were in place.

But that is not the case now. We do not know the significance of reducing HIV viral load for HIV transmission, and current therapies are burdensome in the extreme. Given the fact that HIV prevention can be achieved by behavioral change, there can be no ethical justification for imposing burdensome treatments on persons with HIV. As a consequence there is no justification for mandatory HIV testing to identify people with HIV infection.

Indeed, a much more pressing challenge will be the capacity to foster and reinforce norms of safer sex in the face of undetectable viral loads. In the face of risk that is radically reduced (if not eliminated) what messages can be conveyed about the need to use condoms? And about the responsibility to behave in ways that do not place partners at risk?

Some indication of how the prospects of prevention can affect thinking about HIV testing, policy and practice can be derived from a consideration of the evolving dispute over testing during pregnancy. With the announcement of the results of ACTG trial 076 and the recognition that a radical reduction in the transmission of HIV from infected mothers to their fetuses was possible, some began to argue that all pregnant women should be subject to mandatory testing, if not as a prelude to mandatory treatment—which would be impossible to enforce, short of incarceration, as well as violative of the privacy rights of the mother—then as a way of requiring that a pregnant woman make a decision about whether or not to undertake treatment in the face of an actual diagnosis of infection. Others, most notably some with a long history of advocacy on behalf of women with HIV, argued that the burden of decision making should shift to those who would decline to be tested; hence some asserted that it was time to move on from an informed consent model to an informed right-of-refusal. In part, this debate has been framed by the fact that, at least in the United States, much testing during pregnancy takes place on the basis of presumed consent and that hepatitis B and syphilis screening is mandatory in some jurisdictions.

Despite the palpable shift in the discussion surrounding HIV testing during pregnancy, many advocates and ethicists continue to argue that a move to mandatory or near-mandatory testing for HIV infection is not practical, necessary or ethical. That very high rates of HIV testing can be achieved by voluntary methods is clear. Furthermore, it is argued that coercion is a bad way to initiate a clinical relationship that will require a patient to undertake a complex course of therapy with uncertain effects upon a woman and her fetus which, in any case, might not be infected. Finally, it has been asserted that in the absence of an ethical justification for mandatory treatment, there is no ethical warrant for mandatory testing that could serve to identify infected women.

In summary, nothing in the achievements of the new combination therapies would appear to alter the arguments that first arose with regard to monotherapy with AZT during pregnancy. Indeed, the complexity and burdensomeness of the therapies makes all discussion of compulsory treatment in the interest of the not-yet-born child even more unacceptable than was the case with monotherapy. Proposals for mandatory screening must thus be viewed with considerable skepticism.

Conclusions

It is a striking feature of the global AIDS pandemic that the new combination therapies 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 therapeutic impotence.
Given the current cost of the new drug therapies there is little likelihood that they will become available where they are so desperately needed. And, indeed, given the relative importance of therapy and prevention in nations where the incidence of infection is still alarmingly high, it is unclear that even were they marginally more affordable that investment in such therapeutic agents would be a wise use of resources. This state of affairs underscores the consequence of disease in a world characterized by deep and widening gulf in wealth, 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 an achievement will meet the needs and moral claims of the poorest nations for effective AIDS prevention. Those claims will be harder to press if HIV disease becomes a more manageable and less threatening disease in the richer nations because of advances in antiretroviral therapy.
Case study presentations
Antiretroviral Treatments in Uganda

Elly Katabira

Introduction

Uganda is one of the countries with the highest incidence of HIV infection in the world. It is estimated that by the end of 1996, there were about one and half million Ugandans infected with HIV, many of whom are now showing signs and symptoms of the disease. The universal approach to the care of most of these patients has been the prompt management of their frequent opportunistic infections (OIs) and the aggressive use of readily available and affordable drugs. This kind of approach has been adopted by the Ministry of Health and taken up by many institutions involved in the care of HIV-infected people, such as TASO.

Since this approach was launched in the mid and late eighties, there have been tremendous advances in the treatment of HIV-infected people, particularly in North America and Europe. The advances have been made mainly in the field of antiretroviral drugs where in some countries like the USA they have been associated with improved quality and quantity of life. Through increased media coverage and opportunities to attend AIDS conferences, some of our patients have become aware of these drugs and have been asking how and when they can also use them.

Availability of Antiretroviral Drugs in Uganda

Antiretroviral drugs are not available in government health institutes or those run by religious organizations. Their availability is limited to private pharmacies or from direct ordering from various suppliers outside Uganda.

Zidovudine (AZT) is the most commonly available in pharmacies in 100 mg and 250 mg tablets. Only a few pharmacies stock zalcitabine (ddC) and didanosine (ddI). Protease inhibitors were given excessive coverage during the Vancouver AIDS conference in July 1996, but, being new, they are not imported on a regular basis. Those who need them have to make their own arrangement to get them from outside the country. However, there are a few pharmacies which are willing to bring them into the country but on an individual basis and at an additional price.

Because of the desperation of some of our patients, drugs of questionable quality have been sold by unscrupulous people. This is particularly likely if the selling price is well below the known usual cost. Many unsuspecting patients have been sold ordinary drugs like paracetamol or vitamin capsules as AZT!

Quality of Medical Supervision

In Uganda, much effort has been put in the proper care of HIV-infected people. A lot of training workshops and seminars have been given to those who are involved in the care of these patients. In addition, several books and guidelines have been written targeted at various levels of health workers. In most cases very little emphasis has been put on the use of antiretroviral drugs because they are considered to be out of reach of many patients. However, as more and more people come out who can afford them, situations are arising where doctors are prescribing these drugs without adequate knowledge and skills to monitor them.

Dr Elly Katabira, Makerere Medical School, Kampala
It must be appreciated that patients with HIV disease often take many different medications, including herbs. Thus it may be very difficult to attribute any complications which may arise to a particular drug, including an antiretroviral.

A 32-year old female banking officer was referred to me by a private medical practitioner in town for a consultation. The doctor had been seeing her for the past nine months for various problems including a relentless skin rash. She had been started on AZT 250 mg twice a day four months ago in addition to various creams and antihistamine drugs for the skin rash. In the past nine months of care, she had had one CBC done at the beginning and several screens for malarial parasites and widal tests for typhoid fever. When I saw her she was strikingly anemic with an Hb of 5.4 mg %. When I asked her doctor how long she had been anemic, he said that he had seen her about six weeks earlier when she appeared slightly so but he had thought that it was part of her illness. The patient admitted to me that she had been taking some herbs for the skin in addition to the other drugs but she had not told her doctor. Her hemoglobin improved when the AZT was stopped and she was advised to stop taking the herbs but may not have done so.

Issue of Cost of Care

When AZT came on the market in the late eighties, one of the reasons why it remained unavailable in countries like Uganda was because of its expensive price tag. Even though this initial high price has come down over the years, still many people in Uganda cannot afford to use it for any length of time. Other antiretroviral drugs are also too expensive, particularly the protease inhibitors.

However, the cost of care for HIV-infected patients on antiretroviral drugs is not only restricted to buying drugs. The cost of care also includes that of laboratory tests which are often sophisticated and expensive. Many of these investigations, like CD4 cell count and viral load studies, are only available in one or two places in the whole of Uganda. Many of the doctors caring for these patients are unaware of the need and importance of these investigations and in most cases could not provide them anyway. Similarly, most of the patients do not include the laboratory costs when they assess their financial capability before embarking on the treatment.

The average cost of a monthly course of AZT is about 150,000-200,000 Ugandan Shillings (150-200 USD). A combination regime with a protease inhibitor could cost as much as 1,500 USD a month without consultation and laboratory charges. Most patients who take on this treatment may have enough money at the beginning to carry them through for a few months with hope that their financial situation will improve with time. Also some rely on wealthy relatives and friends to team up and find the money. Unfortunately, many patients who are started on ARVs fail to maintain adherence to the treatment or have to give it up all together because they run out of money after only a few months.

S.L., a medical doctor, developed HIV related symptoms in January 1992. By March 1995 he was getting weaker, requiring frequent 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 his family. Initially his family discouraged him to spend 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 prior to and during the Vancouver AIDS conference.

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

Adherence

No one likes taking pills, particularly in Africa. It is common knowledge among Ugandans that given a choice they will take an injection rather than a tablet. That put aside, taking pills particularly for a prolonged period of time can be a nuisance. Patients on ARVs are often required to take many pills as frequently as 4-5 times a day. HIV infected patients who have to pay a lot of money for their treatment are often very motivated and are very willing to take on gruelling treatment regimes including waking up in the middle of the night. Nevertheless, it is not surprising that many of our patients often miss some doses. Initially they just miss doses, but later they miss the entire day's treatment. The situation is made worse in cases where one may be taking other drugs for various opportunistic infections in addition to their ARVs. Sometimes it is the ensuing conditions like HIV-related diarrhoea and vomiting which makes taking ARV drugs difficult.

A 42-year old successful businessman who had been sick with HIV-related symptoms for two years consulted a physician in town about his condition. He had been sent by a friend for possible introduction of ARVs. He had been treated for tuberculous pleural effusion a year ago. He was getting recurrent fevers and continued to lose weight. Various tests including those for TB, had been done with negative results. His CD4 cell count was 85. After extensive counselling he was started on combination therapy including a protease inhibitor, AZT and 3TC. By the end of the first month the fevers had gone and he had regained most of his weight. Two weeks into the second month he went on a business trip outside the country for ten days. Although he took his medication with him, he did not take it most of the time. He said that he did not want his friends to know that he was taking that many drugs. On return from the trip, he resumed taking the drugs as before but after a week he developed a chest infection for which he is now being treated.

Clinical Experience with ARV treatments

There are enough studies done in the developed countries to support the effectiveness of the commonly used ARVs. Unfortunately, such studies are few in the third world. Ideally one should start on ARVs early enough before severe immunosuppression sets in. However, this is not always possible because the patients who embark on this treatment do not get regular assessment to monitor their immune system. The majority start ARVs after developing serious opportunistic infections even though they may have known their serostatus some years back.

Indeed some of these patients do not start ARVs until their CD4 cell count is well below 50 or even zero! To those who are severely immunosuppressed and with life threatening OIs like cryptococcal meningitis or Karposi's sarcoma, their prognosis remains poor even when they take their treatments (including ARVs) religiously.

In spite of all this, however, patients who start on ARVs with minimal OIs and reasonable CD4 cell count often do well. Some have even resumed regular activities after a few months treatment.

J.K is a 10-year old primary pupil who lost his parents to AIDS five years ago. He developed serious HIV-related signs and symptoms a few years ago which included recurrent chest infections, fevers and skin rash. Six months ago he was started on triple therapy with a protease inhibitor, AZT
and 3TC costing the extended caring family USD 1,500 per month. His CD4 cell count at the beginning was 200. After three months treatment his chest infection and skin rash improved and he was able to go back to school. So far he has adhered to the multiple medications he has to take, some of which require tests which are very unpleasant.

Views on the Use of ARVs in Uganda

Physicians

Here the opinion is divided on the relevance of ARV treatments in Uganda. Some feel that it is unnecessary, unsustainable and too expensive for someone who is going to die anyway. They argue that even if the patient may have enough money at the time when he starts on the treatment, he is bound to run out within six months or so. Some depend on wealthy relatives who may be willing to finance the treatment without appreciating the long-term implications. They suggest that this money may be more usefully invested to take care of the orphans who are likely to be left behind.

Other physicians argue that combination therapy with a protease inhibitor, if properly taken and monitored, improves the quality and quantity of life tremendously. As a result of this, these patients are able to resume work and even plan better for their families. They also add that the natural history of HIV infection is still poorly understood, particularly in Africa. In the early days of the epidemic many people thought that AIDS had an accelerated course such that many of those who were infected died within a few months or years. We now know that this is not true. If combination therapy could extend the life of HIV-infected people to the level of those who are not infected, then no one has a right to deny them therapy if they say they can afford it.

General Practitioners

Many private practitioners in Uganda including those in the city have had no experience with ARVs. However, many expressed willingness to put their patients on ARVs if the patients can afford them. This will incite them to learn more about the drugs if they have to do the monitoring. Unfortunately very few of their patients can afford this kind of treatment.

A few practitioners said that there were scared to put their patients on ARVs as they know nothing about them. They would rather refer such patients to other doctors who have had experience in this field.

One practitioner who said he had two patients on ARVs (one for four months and the other for two months) was impressed by their response. All had gained back weight they had lost and the chronic OIs which were bothering them had disappeared.

Researchers

There has been no recent research done with the current crop of ARVs on the market. However, there are ongoing studies looking at some new drugs yet to be registered. This group of scientists believes that such studies are ethically acceptable even though they know that the final product will not be accessible and affordable for the majority of HIV-infected Ugandans. They argue that the benefits given to those patients in the study duly covers their contribution to global science in the field of AIDS therapy. However, some researchers insist that unless those in the study are given life access to free ARVs under research, then it is not ethical to use them as guinea pigs.
NGO Health Workers

NGO health workers often provide care to a section of patients who are unlikely to be able to afford ARVs. However, some have read about the benefits of these drugs and would like them to be made available to their patients. Many of these Health Workers do not object to their presence in Uganda in the private pharmacies, but would like to see the drug companies reduce their costs to an affordable price. Certainly they would not like the government to import them as essential drugs. They feel that the government should concentrate on making other simple but more useful drugs like painkillers and antibiotics more available. They play a major role in improving the quality and quantity of life of many patients.

MOH

ARV drugs are not included in the list of essential drugs and are unlikely to be included in the near future. The MOH have no objection to research being done on ARVs in Uganda, though they would like to see the participants in such studies indefinitely covered for treatment with the relevant drugs if they turn out to be effective.

People living with HIV/AIDS

Like anywhere else in the world PLHA become desperate as their disease drags on and gets worse. Those who are on ARVs are grateful for the improvement they get from the treatment. However, they feel the financial strain associated with maintaining the treatment. Those who are more vocal feel that the drug companies are there to exploit them and they resent this. They feel that drug companies should be more considerate and reduce the costs to make their products affordable to more people.

On the other hand the many patients who are not on ARVs also wish they could be on it but for free. They would rather spend the money on looking after their families and planning for their future when they are gone. It does not make sense to think of ARVs when more often than not they cannot even afford to buy a course of antibiotics.

Conclusion

Currently there is little experience about the use and effects of ARVs in Uganda. The available experience is still anecdotal and is yet to be properly documented. The information available so far indicates that they are equally effective among our patients. What is clear so far is that compliance is still a major problem due to various reasons and that the drugs are too expensive. It would be unrealistic to recommend that these drugs be made available now using public funds. Governments, however, should make it feasible to import them easily through the private sector and also provide training for doctors so that they can use them properly.
National Antiretroviral Programme: Thailand’s Experience

Chaiyos Kunanusont*

Background

Following a decision by the National AIDS Committee (NAC) in 1992, the Ministry of Public Health (MOPH) made a commitment to supply antiretrovirals (ARV) to low income, HIV infected patients in order to provide equal access to treatment for people with HIV/AIDS. The budget increased from 35 million baht (US$ 1.4 million) in 1992 to about 300 million baht (US$ 12 million) in 1996. The price of AZT decreased dramatically to 8 baht per 100 mg capsule due to increased competition among manufacturers and government bulk purchase. The pharmaceutical company of the Thai government started manufacturing and provided AZT to the MOPH at about 9 baht a capsule.

Figure 1  Budget for antiretrovirals and price of AZT (per 100 mg)

With the exponential increase in cases and also the rapid advances in combination therapy, benefits from the programme were to be expected. In 1994, the MOPH consulted the World Health Organization, UNAIDS and the World Bank to provide experts to investigate the cost-effectiveness of the programme. The team reviewed epidemiological projections, clinical efficacy, policy alternatives, and economic models to review rational use of ARVs in Thailand.

Review of Rational Use of ARVs

Epidemiological projections

Epidemiological projections of caseload served as the backbone of the study. The review team used the medium intervention projection model of the National Economic and Social Development Board, which relied on assumptions relating to situations and interventions in 1994. It is estimated that there will be approximately 50,000 new cases of AIDS and 60,000 new cases of symptomatic HIV during the period 1995 to 2005. Taking into account disease progression and survival rates, the number of cases were transformed into person-years of caseload. There will be approximately 50,000-60,000 person-years of AIDS and 100,000-120,000 person-years of symptomatic HIV each year from 1995 to 2005.

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**Clinical efficacy**

The team examined six possible alternatives for anti-retroviral treatments for adults and two alternatives for reduction of mother-to-child transmission of HIV infection. Clinical efficacy in terms of survival gain was derived from international journal articles on adult treatment regimens. The efficacy of the use of ARVs for reduction of transmission from mother-to-child was derived from the results of the ACTG 076 study. Absolute survival gains of 0.89 to 1.45 years were associated with concurrent AZT+ddI or AZT+ddC therapy for symptomatic patients (Table 1).

Table 1. Survival gains (in years) by treatment regimens

<table>
<thead>
<tr>
<th>Treatment regimens(*)</th>
<th>lower limit</th>
<th>upper limit</th>
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<tbody>
<tr>
<td>1. No anti-retroviral therapy</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>2. AZT for AIDS</td>
<td>0.35</td>
<td>0.75</td>
</tr>
<tr>
<td>3. AZT then ddX switch for AIDS</td>
<td>0.35</td>
<td>0.75</td>
</tr>
<tr>
<td>4. AZT+ddX concurrent for AIDS</td>
<td>0.35</td>
<td>0.79</td>
</tr>
<tr>
<td>5. AZT for symptomatics</td>
<td>0.35</td>
<td>0.86</td>
</tr>
<tr>
<td>6. AZT then ddX switch for symptomatics</td>
<td>0.35</td>
<td>1.20</td>
</tr>
<tr>
<td>7. AZT+ddX concurrent for symptomatics</td>
<td>0.89</td>
<td>1.45</td>
</tr>
<tr>
<td>8. AZT for symptomatics</td>
<td>0.35</td>
<td>0.86</td>
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</table>

* Universal treatment of opportunistic infections was assumed.

**Source**: Jos Perriens, Ken Hill (personal communications)

**Cost analysis**

Effectiveness to cost ratio ranged from 4 (AZT for asymptomatics, regimen #8) to 20 (AZT then ddI or ddC switch therapy for AIDS, regimen #3) quality-adjusted life years per one million baht. Regimen #3, on the assumption of complete coverage (i.e. treat every case), would cost more than three times the government AIDS prevention and control budget. If patients had to pay for treatment themselves, about 70% of the population would not be able to purchase regimen #3 from their nonfood expenditure. Economic analysis showed high cost, low benefit and limited affordability with this regimen.

**Thailand's response**

Recorded data on coverage and adherence were reviewed. Most patients were non-adherent and the programme covered less than 30% of all symptomatic HIV and AIDS cases presenting for care. Low effectiveness is probably due to both low coverage and low physician/patient adherence. In 1996 the MOPH initiated a policy to supply ARVs primarily to adherent physicians and patients. Increasing the budget to cover low income groups, for all AIDS related conditions, would allow the demand for ARVs to be met. However, the treatment of HIV/AIDS has not been the first priority for many hospitals/institutions.

Inadequate adherence on the part of both patients and physicians could be due to lack of information. Another reason could be the lack of team work across the continuum of care to support patient adherence. The Ministry is expected to solve this problem by setting up a network to supply ARVs.

Worldwide, HIV/AIDS drug development is expanding as rapidly as the epidemic itself. Phase III trials require several thousand HIV positive subjects. Although the caseload in Thailand is a great burden for the nation it can also be seen as an opportunity to set up networks of patients for clinical
trials. In this way, people living with HIV/AIDS (PLHA) participating in clinical trials get better access to care, physicians increase their knowledge of ARV treatments and the government saves on its budget.

Clinical Trial Networks in Thailand

Ministry of Public Health clinical trial networks

The Ministry expected to solve adherence problems by setting up a network for anti-retroviral supply. Certain hospitals/institutions were selected to ensure good participation. Other hospitals received ARV supply by quota. Care providers in network hospitals were invited for Good Clinical Practice training and ARVs were supplied for an agreed number of cases.

The network, in the first phase, included 45 hospitals in 20 provinces throughout the country. Participating sites were selected through a careful screening process. Data from a survey on a Day Care Development project in 1995 in 229 hospitals were reviewed to identify eligible hospitals for the clinical trial network. Among 107 hospitals which were ready to participate, 56 joined the investigator workshop and 32 confirmed their decision to participate. Members of the expert group on HIV care were invited to participate and their hospitals were also included. A total of 45 hospitals in 20 provinces in Thailand were selected.

The first protocol was a randomized open label study in 2,000 ARV naive adults comparing AZT+dld to AZT+ddC. Endpoints are measured clinically (disease progression, Karnofsky score), and with laboratory markers (CD4, total lymphocyte count). Adherence is determined from follow up. The second protocol was an open label study of AZT+dld+Saquinavir in 85 subjects in three hospitals. More protocols for more participating sites are being considered. All trials in 1997 aim to build up infrastructure for phase II/III drug and vaccine trials.

Clinical trials of perinatal interventions were also initiated. The Department of Communicable Disease Control worked with the Department of Health to implement different short course regimens of AZT for HIV positive pregnant women and their babies. Powdered milk was strongly recommended for babies born to HIV positive mothers. Participating hospitals were enrolled according to their preparedness for the protocols in terms of medical, psychological, and social care. Official enrolment of cases for the trials will be in June 1997. However, since 1995 several hospitals have provided AZT independently. A central supply of AZT + powdered milk would encourage researchers to work together and would facilitate setting up of the network. The MOPH network jointly collaborates with HIVNAT (HIV Netherlands, Australia, Thailand) on several protocols namely, AZT/ddC, dld/d4T, on variable doses, and possibly on Interleukin-2 (IL-2) soon.

Lessons learned

An important lesson that the Thailand HIV/AIDS Prevention and Control Programme learned was the setback impacts of budget development. The second lesson was the importance of favourable collaboration between government and private agencies. The third lesson was the importance of psychological and social care as determinants of adherence to therapy.

A continuous supply of antiretrovirals, on the one hand, has encouraged physicians to take care of HIV/AIDS patients, but on the other hand, has discouraged many hospitals/institutions from setting up their own budget. Several hospitals depended on the Ministry of Public Health ARV supply so they tended to refuse to provide care for HIV/AIDS patients if the supply was discontinued.
Since the first year of central supply of ARVs, the AIDS Division had searched for a common concern between the government and pharmaceutical agencies. It turned out that drug resistance associated with irrational use of ARVs was the greatest concern. Training and refresher courses have been developed to disseminate knowledge and to share experiences on how to use antiretrovirals properly. Urgent messages have been carried back and forth by government officials and pharmaceutical representatives. Rapid feedback facilitated fine tuning of the programme. A clearer picture of what was going on in rural hospitals brought up the tight relationship between the Thai CDC and the frontiers. Also, it was perceived that the government has demonstrated its concern to support HIV/AIDS management. People living with HIV/AIDS appealed to the government and developed more friendly attitudes to drug companies when the price of AZT went down. Drug companies then spent a fair amount of their budget on community support and clinical trials. Unregistered drugs have been made available on compassionate grounds.

Infrastructure to support clinical trial activities includes system management for manpower, budget, and technological readiness. The supply of ARVs alone is not enough to provide optimal benefit for PLHA and their families. Physicians must keep up with the “state-of-the-art” of ARV treatments and then translate their knowledge into day to day practice. The counselling process increases patient adherence and psychological well being.

Clinical trial activities require system development in (1) medical care, (2) psychological care, and (3) social support for the continuation of therapy regarding place (in hospitals and communities) and time (follow up).

**System Development**

The Thai CDC allocated a total of 114 million baht (US$ 4.6) for the project “System Development for HIV/AIDS Care”, which has enrolled 83 hospitals/institutions as of 1997. All 45 hospitals in the MOPH clinical trial network are automatically enrolled. The primary aim of the system development project is to ensure the existence and continuation of medical, psychological, and social support along with human rights protection for PLHAs and their families (CCC-Comprehensive Continuum of Care). Each of the 83 hospitals/institutions participated in five regional workshops and proposed a plan of action reflecting its own needs and the needs of the Thai CDC, based on each hospital/institution’s responsibility in the local epidemic situation. Each plan of action is translated into a proposal and signed by the local authorities. The proposals must fit the system development philosophy in order to be approved. Up to mid April 1997, 20.2 million baht has been granted to 54 proposals in 29 provinces.

**Discussions and Conclusions**

Thailand is one of a few countries where government supply of antiretrovirals has been institutionalized. The programme has positive and negative impacts on HIV/AIDS care. A rapid response by the government has allowed more PLHA to get access to care which subsequently has created more work for the health care system. Careful evaluation has identified the need to develop a comprehensive continuum of care for HIV/AIDS. A central supply of antiretrovirals binds participating hospitals together in the clinical trial network.

The evolution of anti-retroviral supply in Thailand has resulted from the simultaneous and rapid growth of the epidemic, coupled with rapid economic growth, immediate responses, and demand for drug trial platforms. The explosive epidemic has aroused public and private concern. Economic growth allowed the government to supply antiretrovirals continuously. Scientific advances have facilitated new anti-retroviral development and increased the demand for clinical trial sites/subjects.
Caseloads in Thailand have been perceived as a burden but it can be an opportunity if the network for clinical trials is functioning well.

Lessons learned from the programme should be disseminated to neighbouring countries. Thailand has walked a few steps forward, in terms of its antiretroviral programme, compared to other countries in the region. Our experiences should be studied carefully by developing countries especially those on our borders in similar situations, so they can enjoy the benefits and avoid possible pitfalls.
Case Study

Naiisiadet Maina

In 1988, after several attempts by three different doctors to treat a persistent flu, my fourth doctor suspected that I might be HIV+ and proceeded to test me by removing some tissue from one of the many swollen lymph nodes on my neck. The test was positive. My mind just would not come to terms with this diagnosis and I had four additional tests. The verdict was the same in all the tests, and the challenge of living with AIDS began.

At that time doctors knew very little about HIV/AIDS and therefore things like pre-test and post-test counselling were things unheard of. My doctor reassured me constantly that I could live as long as I wanted to if I took charge of my life and lived positively. The positive diagnosis made very little sense to me as I had heard about AIDS, but AIDS was not a disease for married women as far as I knew. I was thus in a stage of denial which lasted eight years. During this period I was very lucky and my health was excellent. My husband was tested as a result of my diagnosis shortly after me and he too was confirmed HIV+. For him this meant death, and indeed two and half years later he did die from a number of AIDS related conditions. Before his death on December 1, 1990, he was hospitalised for a period of six weeks at which time he was put on AZT and Kemron. Our doctor having felt that my husband's deteriorating condition would affect me adversely, put me on these two drugs as well. The only way I was able to afford these drugs was because the doctor incorporated the cost into my husband's hospital bill. After he died, I was unable to access these drugs due to their high cost. I therefore took them for only three months and then had to stop. I cannot say whether these drugs helped in any way, because up until this point I was still in denial and I felt so long as I continue ignoring my condition it might just disappear. This was not to be the case as I soon found out.

In 1994, I noticed that I was constantly getting a rash all over my body, and particularly concentrated around my face. Several attempts to treat this condition proved fruitless and I incurred high medical bills which I covered with a medical plan I had with the organisation I worked with. Unfortunately, the high bills raised flags, and soon the organisation decided to investigate my medical condition. They found out I was HIV+ and soon after, I lost my job, marking the beginning of even greater challenges in my life. My health condition started a downhill path.

The rash increased, Candida and herpes constantly nagged me, and I was in no position to afford treatment. There was never a day that passed that I can say I was feeling well as persistent colds were the order of the day for me. With no income and two young children to bring up, I knew unless I did something drastic, death was nearer than I had ever imagined. I decided I was not ready to die just yet. With the skills I had, I felt that I could get a job with one of the AIDS support organisations. Luckily, there was a vacancy and I was employed soon after as an administrator. At first, I kept my status a secret, but after some time I realised three quarters of the employees were HIV+ and slowly, I started talking with my colleagues, listening to their experiences and sharing mine. Talking about my condition became easier and easier such that when meetings with donors took place for fund-raising, I would be on the front line trying to sell our proposal using my first hand experience.

I believe desperation and fear of death, with the result that my children would grow without a mother were the main reasons I decided to come out. After about two months I actually started enjoying what I was I doing, and I realised that accurate information regarding prevention and care of

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HIV/AIDS was of great import. I made it a point to read all available literature, newsletters and magazines about HIV/AIDS. I attended conferences, workshops and seminars looking for information on the latest treatments. Of course having known that drugs are available to treat my condition and therefore prolong my life, my constant thought was how could I access these drugs which were not sold in Kenya. I knew AZT was readily available in Kenya, but its cost was way beyond what I could afford.

Other drugs for opportunistic infections were also available, but again I could not afford them. I then decided to tell my siblings who live in the USA about my condition. One of my sisters was very concerned, and immediately started looking for antiretrovirals, and other drugs to treat opportunistic infections. She solicited for drugs through AIDS support organisations across the United States, getting drugs from those patients who no longer needed them for one reason or another. Her efforts paid off. She managed to get a six month supply of AZT and 3TC. Now that I had the drugs, the biggest question on my mind was, which doctor in Kenya knew enough about these drugs to monitor my progress. Finance was one of my biggest constraints, therefore I could not afford to pay a doctor, and also I could not afford to get tests such as a CD4 count and liver function analysis done. These tests are necessary to mark the starting point of treatment, and as indicators of the efficacy of the drugs.

All the above was happening in 1995, the same year I joined Women Fighting AIDS in Kenya (WOFAK), an AIDS support organization for women, as programme officer. Here I received greater care and compassion than in the previous organisation. In return, I did and still do all I can for WOFAK as a volunteer. It is through WOFAK that I met the doctor whom I felt I could trust to start me on the AZT/3TC combination. The doctor felt that due to the toxic nature of AZT she would prescribe a lower dose of 200mg a day and 300mg 3TC a day. I had no acute side effects, but I do remember having constant fatigue during the first month. Also, enough nutritious food was very important; otherwise the drugs taken on an empty stomach would prove very noxious and debilitating. Of course nutritious food was not always available due to insufficient funds, but I made all attempts to eat well for I knew without good food then the drugs might do more harm than good. Along with these drugs, I took Chinese herbal medicines such as Astralegus, Legustrum and Tea Tree. These were primarily used to boost my immune system and treat the persistent itch. As with the antiretrovirals, my sister sent the herbal medicines from the US along with many books on Chinese medicine and treatment. Once I tried some herbal medicine from a doctor who had been recommended to me by a friend in Kenya to treat a cold. I stopped taking Septra which I had been taking since the previous year as prophylaxis for PCP. The results were disastrous, I came down with pneumonia. I learnt never to take drugs/herbs which have not been tested and used by others to confirm their efficacy.

I recovered from the pneumonia after two weeks at home. I refused to go to the hospital because first, I could not afford it and two, I felt I would never leave the hospital alive. During this time friends, family, colleagues, and my parish priest offered me constant support. They came to visit me constantly. Never was I at home alone. This was the closest I came to being counselled. Most counsellors I met did not seem fully equipped with counselling skills, and I therefore found it difficult relating to them.

In January 1997, my sister came to Kenya to visit having heard that I had come down with pneumonia. She brought AZT, 3TC and even Indinavir! I was impressed at her tenacity to get these life saving drugs. She urged me to start the triple combination therapy, but I was terrified to start on a protease inhibitor. I had read about the strict regimen it requires as well as the fact that if I developed resistance I would have no other option of a protease inhibitor at my disposal. Which doctor was conversant with this new drug in Kenya? Where could I do a viral load test? These were questions that came to mind, that needed answers before I committed myself to taking this combination. From my reading I knew starting on a protease inhibitor was a serious decision that I must make but since I felt that our doctors did not have the knowhow to monitor my progress, I was not ready to start the triple combination therapy.
Shortly after my sister’s visit, I went to the United States where she and I felt that I would get the best treatment. It was not easy getting into the United States, but somehow God made it possible. The first astonishing thing I noticed about the USA was that one could get treatment free of charge! I could not believe this. Especially when I remember my brothers and sisters in Kenya are dying from lack of drugs for opportunistic infections. I was very interested to know how their system worked, and I came to realise that there was total commitment and support from the government, along with other HIV/AIDS agencies, and even more important, that the American people have made this their problem and will put in as much time and energy to win the battle against AIDS. The drugs are accessible to patients, the doctors are well trained, and hospitals and laboratories are equipped and functional. There is a strong structure connecting the patients, doctors, counsellors and social workers with the sole intention of prolonging the life of the patient as well as making it fuller.

In Kenya it is important that both the government and the people themselves take a more proactive role in the battle against AIDS. For unless there is a concerted effort by the key players, intervention programs will not have the intended impact. It is true that we desperately require drugs for opportunistic infections and antiretrovirals. We must also have effectively trained service givers including doctors, nurses, counsellors, social workers etc. Functional hospitals and equipped laboratories are of paramount importance if we are to give effective service to those infected with HIV. Finally, of greater importance than all else is the commitment and transparency from all key players, and even greater support from the government. With these tools I believe we in Kenya can make a difference in treatment and care for those infected.

Since I went to the US, I am still on the AZT/3TC combination although the AZT dosage has been increased to 600mg per day. From the great results achieved it appears that I was drug naïve. My CD4 count went up from 94 to 216 and viral load went from 295,000 copies to undetectable levels in a period of one month. The above combination has worked so well, it has not been necessary to put me on a protease inhibitor yet. Even just accessing the antiretrovirals, which are not as expensive as the protease inhibitors, would be very big step forward in improving the quality of care for HIV+ patients in Kenya. The regimen for taking these is not quite as rigid as with the protease inhibitors, and they still leave various options if resistance does develop. It will be of utmost importance to educate patients on adherence. It is not enough to take the drugs on time; nutritious meals are also necessary and often are not within reach of the majority of the patients. The socio-economic problems must be addressed so that in the end these drugs are not wasted but serve to improve the life of those who are HIV+.

Together with the above regimen, I also took up alternative therapy, which primarily included acupuncture and massage. These have been useful, especially for stress reduction. I have continued to take Chinese herbs to further boost my immune system. Family, friends, colleagues have given me tremendous support in my trials enabling me to live these ten years. Again this is a very important aspect of care that we must not ignore. Treatment and care of an HIV patient involves several components which are all dependent on each other to get the best results. You cannot address one issue and not the others and expect to get the desired results. Thus as we try to access drugs for people in developing countries let us realise getting the drugs alone will not solve the problem. A concerted effort must be made to address the whole continuum of care.

With the current antiretrovirals I am taking, I realise there is no stopping until a cure has been found, but these are the things in my life I have to come to accept. These are the challenges that I have come to learn to deal with. I try not to dwell on negative thoughts, and instead think about all the interesting things that I can do. I take my drug regimen very seriously because I am fully aware of the repercussions of missing a dose. I realise this will be difficult for many of our patients in Kenya, but once they have been provided with accurate information regarding the importance of adherence, I believe HIV+ patients will react positively and take the drug regimen with the seriousness it warrants. It will not be easy, but it is possible.
It makes me sad that I had to literally run away from my country to access treatment. I would like to see these drugs available to my brothers and sisters at home. Ways and means of reducing the cost of these drugs should be looked into. So as we sit here today, I believe with a committed mind, a compassionate heart and one voice, we can and will find a way. Let us listen to the cries, and let us respond with compassion. The ball is in our court here, today, let us take the challenge now. Thank you.
Implications of Antiretroviral Treatments
Improving the Quality of Life - a Matter of Survival

Jairo Enrique Pedraza*

Quality of Life: I have been living with AIDS since 1988, my quality of life has been influenced and changed by the therapies I've enrolled in. I have had four bouts of pneumonia, PCP; Cytomegalovirus (CMV); Retinitis in my right eye and CMV encephalitis; Herpes Zoster; Cryptosporidiosis; Epilepsy.

As a patient, many times I have not complied. The word in itself is very disempowering. To comply means to do what you are told that you must adhere to. It leaves very little space for self-determination, autonomy or self responsibility. It is just a word but it can make a real life difference in how something is understood, and whether you decide to comply or not.

HIV diagnosis to me has meant being labeled by the virus I carry rather than by my individual traits. I still want to love and make love. I want to work and be productive and contribute to society. I have dreams, feelings. I still have dreams, I want to finish my career, I have places to go and family to see, nephews, nieces who love their uncle, I want to see them grow. I want to be with my mother in Colombia. I have dreams, my family has dreams. But I also have HIV. HIV has become not only a nightmare, but a social stigma since I'm seen as the person with AIDS not as Jairo, the person.

Today I don't have any answers to the questions before us. I do have many, many additional questions that I ask myself everyday, even in my dreams. AIDS for me is not a 9 to 5pm issue. It is a 24 hours around the clock issue. To me it is living with AIDS, dreaming with AIDS, having nightmares with AIDS. The questions today are:

Starting HIV Treatment: When, Why, Where, How, Which and What if?

When-to-start treatment: Do I start when I have symptoms? I was raised to expect that for a headache I should take an aspirin. If I had a cut, I will put coffee powder in the cut to stop the bleeding. I was never raised to believe that if I felt well, I had to start treatment, which may, at times make me feel sick. When I did start treatment, it was with the hope that if the treatment was palliative it was effective and I would be well.

When to start treatment: When laboratory exams indicate I must. My choices of therapy are decided according to laboratory results. I always pray before I go to get my CD4 count test, and according to the results my mental stability is determined. There are occasions in which my T-cells have dropped to a single digit and because of it my psychological condition has deteriorated, leading to the point of considering suicide, as the only option. My CD4 count results and viral load results are like my bank financial statements. I worry when there is a big debit, when too much has been taken out and I worry when through treatment, I don't deposit enough back into my system and this means dividends have not been paid.

Why start treatment: Should I start treatment because I want relief of a pain and have no alternative, or because through education, knowledge and empowerment I recognize the importance of doing so, or should I start treatment just because I'm told to do so. This raises questions of who is in charge of my treatment: myself, my health care provider, or both.

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Where: The decision when to start treatment is influenced by where I live and under what conditions. I live in a developed country, I'm a legal citizen and I have insurance, I'm one of the fortunate few. If you live in a developed country and don't have citizenship there is no access to treatments, you are considered a second class citizen, who does not deserve access because of your immigration status.

My personal country mobility is highly affected by access, my human right to move is defined by access. I'm a professional, if one day I was to apply for a job, it will be determined where I would go only if there is access to the treatments. In some countries the most basic HIV treatments are not available, we are talking about basic prophylaxis such as bactrim for pneumonia, which is very inexpensive.

Some of the most important elements when considering treatment.

- Effectiveness of the treatment
- Side effects
- Duration of the treatment
- Autonomy for decision-making
- Knowledge and informed decisions
- Self empowerment, Self image and Self esteem

Things I keep in mind when talking about therapy:

- What if I become intolerant, to certain medications: the choices are even fewer.
- For how long will I continue having access to the treatment.
- Viral strains become resistant to therapies.
- Living with HIV and epilepsy limits the choices of my treatment because some medication, such as Foscarinet, can induce seizures.

There are certain sectors of society that have different needs:

- Pediatric. Children living with AIDS, for whom there are very few approved treatments.
- Women. Manifestations of AIDS and opportunistic infections are different than men.
- Substance users, homeless, people in prisons, children of the streets, sex workers, hemophiliacs and others.
- All regions of the world have particular diseases with their specific interactions with the HIV virus.

In developing recommendations on adherence or compliance one must consider people's lifestyle. If you are talking about people living with AIDS who are substance users, homeless, people in prisons, children of the streets, sex workers, hemophiliacs, there are many issues that should be taken into consideration when developing compliance guidelines. It should be kept in mind that the relationship between you and your health care provider is a team effort.

Following are some recommendations for a minimum standard of care from my perspective as a person living with AIDS:

* Diagnosis, treatment, and prophylaxis of opportunistic infections
* Antiretroviral therapy
* Counseling and support

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* Psychiatric care
* Access to a health care team that should include: oral care, vision care, etc.
* Adequate nutrition needs
* Information on available experimental non-allopathic medicine
* Palliative care
* Support to reference groups such as: domestic companion, siblings and parents
* Fulfillment of spiritual needs

We must join in a meaningful collaborative effort between international agencies, People Living with HIV/AIDS and people affected by AIDS, you and I together. I invite you to roll up your sleeves, let's set aside the political agendas, let's set aside the desire for power control and the hunger for recognition, let's work together because our lives and those of our brothers and sisters depend on the outcomes of these meetings. Let's not allow bureaucracies to stand in our way. Time is precious to a person living with AIDS, time is something we cannot afford to loose. Let us involve the private sector, but not only as a donor but as an affected sector as well.

To the pharmaceutical companies we must demand price control, reduction in the price of the drugs. We are not asking for left-overs or for free medications, we are asking for affordable products that our governments can pay in order to make the basic HIV treatments available to all.

To governments that have embargoes which do not allow for the purchase of life-saving medications, I say shame on you. As an international community we should expose such human rights violations. No government should have policies that do not permit the purchasing of essential medications for saving lives in another country.

I would like to thank you, UNAIDS and WHO for inviting me. It is imperative that people living with AIDS always be present at these meetings, that we participate and contribute in a meaningful way and that priority be given to our recommendations. A very special thanks to Dr Dorothy Blake who always has shown compassion and care for those of us living with HIV and AIDS, Dr Blake has always considered communities as the most important partners in the fight against AIDS.

I would like to close by reading the following statement:

On December 1, 1996 World AIDS Day was celebrated, the theme was "One World, One Hope", but the world will remain without hope unless we all work together to develop a concrete action plan which will provide treatment and care access for everyone. We must tear down the wall between those who have access and those who do not. If we are truly "One World, One Hope", we must implement actions to promote better care, treatment and compassion for the millions of women, men and children around the world living with HIV and AIDS.

Let us renew our commitment to those who are still here and long for a cure. As we rejoice in the new treatments and developments of HIV and AIDS research, we must fight stronger and work harder than ever before to make them available for everyone and not just for the few fortunate.

Thank you, Mr Chairman.
Informal Consultation on
The Implications of Anti-retroviral Treatments,
29-30 April, 1997
Conference Room A, WHO/HQ Geneva

Agenda

Tuesday, 29 April 1997

08:30 - 09:10 Opening

Dr Hiroshi Nakajima, Director-General, WHO
Dr Françoise Varet, Assistant Director-General, WHO
Dr Peter Piot, Executive Director, UNAIDS

09:10 - 10:45 Panel: State-of-the-Art

09:10 - 09:30 Clinical Use of ARVs
09:30 - 09:35 Point-of-view
09:35 - 09:55 ARVs and Compliance
09:55 - 10:05 Case-study: Quality-of-Life
10:05 - 10:15 Case-study
10:15 - 10:45 Plenary Discussion

10:45 - 11:15 Coffee

11:15 - 12:25 Panel: Resistance and Laboratory Monitoring

11:15 - 11:30 ARVs and Resistance
11:30 - 11:35 Point-of-view
11:35 - 11:50 ARVs and Laboratory Monitoring
11:50 - 11:55 Point-of-view
11:55 - 12:25 Plenary Discussion

12:25 - 13:30 Lunch
13:30 - 15:05 Panel: Health Systems

13:30 - 13:45 ARVs and Cost-benefits
   Dr Nicholas Prescott
13:45 - 14:10 ARVs and Health Systems
   Dr Charles Gilks
14:10 - 14:15 Point-of-view
   Dr Jonathon Quick
14:15 - 14:20 Point-of-view
   Dr Teguest Guerma
14:20 - 14:25 Point-of-view
   Dr Kevin De Cock
14:25 - 14:35 Case-study: Thailand
   Dr Chaiyos Kunanusont
14:35 - 15:05 Plenary Discussion

15:05 - 17:05 Panel: Maternal-Child Transmission and Counselling and Testing

15:05 - 15:30 ARVs and Maternal-Child Transmission
   Professor Glenda Gray
15:30 - 16:00 Tea
16:00 - 16:15 ARVs and Counselling and Testing
   Dr Rossana Ditangco
16:15 - 16:25 Point-of-view
   Dr Catherine Hankins
16:25 - 16:35 Case-study: Brazil
   Dr Pedro Chequer
16:35 - 17:05 Plenary Discussion

17:30 Reception - WHO Restaurant

Wednesday, 30 April 1997

08:30 - 09:30 Panel: Ethics

08:30 - 08:40 Case-study: Uganda
   Dr Elly Katabira
08:40 - 08:55 ARVs and Ethics
   Professor Ron Bayer
08:55 - 09:00 Point-of-view
   Professor Hakima Himmich
09:00 - 09:30 Plenary Discussion

09:30 - 12:30 Group Discussions

10:30 - 11:00 Coffee

12:30 - 13:30 Lunch

13:30 - 15:30 Plenary Discussion

15:30 - 16:00 Tea

16:00 - 17:00 Closing Session

   Summary
   Professor Pedro Cahn
   Closing Remarks
   Dr Fernando Antezana

Organized by the Office of HIV/AIDS and STDs (ASD/WHO)
with the support of UNAIDS
Informal Consultation on
The Implications of Anti-Retroviral Treatments,
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Conference Room A, WHO/HQ Geneva

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