



safe and effective

use of antiretroviral treatments in adults

with particular references to resource limited settings





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ACKNOWLEDGEMENTS

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The WHO Initiative on HIV/AIDS and STI acknowledges the following individuals who reviewed the draft text and provided helpful comments and suggestions:

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INTRODUCTION

In April 1997, WHO and UNAIDS held an Informal Consultation on the Implications of Antiretroviral Treatments for HIV/AIDS, with the objective of providing policy guidance on major issues relating to the use and provision of antiretroviral drugs.¹ As a follow up activity to this consultation, a set of nine *Guidance Modules* on several aspects of antiretroviral treatments was produced.² Guidance Module number 4, entitled **Safe and Effective use of Antiretroviral Therapies**, provided guidance primarily to clinicians, counsellors, and managers of clinical services. Policy makers, people living with HIV/AIDS (PLHA) and decision-makers in national referral and district hospitals as well as training institutions have also found this guidance module very helpful. The module reflected the published standards of care and the consensus of participants at the time of the consultative meeting in 1997.

Treatment guidelines need to be regularly updated to take into account evolution in knowledge and experiences from different healthcare settings. There is today a much better understanding of the biological basis for antiretroviral therapy (ART) and clinical research has provided consistent data on its effectiveness. The adherence difficulties and adverse effects associated with some of the antiretroviral drug combinations are better understood and regimens that are easier to take are

being developed. There is also an increasing body of knowledge on the therapeutic implications of antiretroviral drug resistance. A variety of international treatment guidelines have been developed to keep clinical practice as much as possible in pace with the data emerging from basic and clinical research.

Clinical guidance for the use of ART must take into account the profile of patients seeking care as well as the capacities of the healthcare setting in which this care is being delivered. Low and middle-income countries have requested recommendations for the provision and monitoring of ART that are more directly relevant to their resource limited settings than the published International Guidelines. In response to this requirement, WHO in collaboration with UNAIDS and the International Aids Society (IAS) organised a technical consultative meeting, in February 2000. This consultation brought together experts in HIV/AIDS care and HIV clinical research from industrialised countries and developing countries, to analyse available scientific evidence and discuss contextual issues relating to the safe and effective use of antiretroviral therapies in resource limited settings. This guide is a result of the discussions and recommendations of the February 2000 consultation.

In section one, the principles behind current use of antiretroviral drugs for the treatment of HIV-1 infection are outlined. This section refers to existing international recommendations.

1. **The Implications of Antiretroviral Treatments.**
Informal Consultation – April 1997. WHO/ASD/97.2.
2. **Guidance Modules on Antiretroviral Treatments.**
WHO/ASD/98.1; UNAIDS/98.7.



Several factors that relate to the profile of patients seeking HIV care in resource limited countries may influence the choice and the outcome of antiretroviral therapy:

- the vast majority of patients are currently treatment naive because antiretroviral drugs are usually not available through the public sector and are poorly introduced into private markets.
- most patients have advanced stage HIV disease at the time treatment is initiated because in the absence of wide spread counselling and testing, diagnosis is often delayed.
- patients in resource poor countries are more likely to have co-existing morbidity such as anaemia, malnutrition as well as tuberculosis and other medical conditions, which may act in concert to affect the choice of therapy and the considerations on the potential spectrum of drug interactions and drug toxicity.
- the majority of patients are in a low-income bracket and because antiretroviral drugs are not usually provided free of charge, financial constraints are a common cause of treatment interruptions and of further delay in initiating therapy.

Within many resource limited countries there are “sites of excellence” where small scale ART programmes have been implemented. Nevertheless, inadequacy of healthcare services in terms of consistency of supplies and quality assurance of laboratory support as well as a scarcity of trained clinicians, are characteristic of most resource limited settings. Experiences with the use of ART in these settings, however, continue to accumulate and there are important lessons to be drawn from them.

In section two of this guide, some national ART programmes and some pilot initiatives from six low and middle income countries are described.

In section three, discussions and recommendations on the use of antiretroviral drugs in resource limited settings, for the treatment of HIV-1 infection, are presented.

The participation of patients in decision-making processes is crucial to the outcome of any treatment programme. People living with HIV/AIDS (PLHA), from resource limited countries participated in this consultation and their contributions on adherence issues and on the psychosocial support needs of patients form an important element of the contents of this guide.



SECTION ONE PRINCIPLES OF ANTIRETROVIRAL THERAPY (ART)*

1.1. BACKGROUND

Data published over the last two years in Europe and North America, from clinical trials and observational cohorts, provide convincing evidence of the beneficial impact of combination antiretroviral therapy on the morbidity and premature mortality from HIV infection. This benefit is mainly due to a reversal of the progressive immune deficiency that is characteristic of HIV infection and to effective restoration of the immune system’s reactivity to HIV induced opportunistic infections (OIs).

The course of many OIs has been altered by widespread use of effective ART. Previously untreatable OIs like *cryptosporidiosis* and AIDS defining illnesses like *Kaposi’s sarcoma* may resolve without specific treatment and the clinical progression of complicated OIs like *cytomegalovirus* and *atypical mycobacterial* infections may be halted and/or reversed. As an extension of the benefits of effective ART, criteria for the discontinuation of chemoprophylaxis against *pneumocystis carinii* pneumonia, which in the past was a lifelong intervention, have been introduced into current practice guidelines. In time, HIV infection may therefore be considered as a chronic disease manageable over the course many years.

* Published guideline documents that are cited in this section:

1. **Antiretroviral Therapy in Adults.** Updated Recommendations of the International Aids Society, USA Panel. JAMA, January 19, 2000 – Vol. 283, N° 3.
2. **Guidelines for the use of antiretroviral agents in HIV – infected adults and adolescents.** US Department of Health and Human Services (DHHS) and Henry J. Kaiser Family Foundation. Issued January 28 2000 available online at: <http://www.hivatis.org/>.
3. **Guidelines for the prevention of opportunistic infections in persons infected with HIV.** USPHS/IDSA, MMWR 1999; 48 (No. RR-10).

The approach to antiretroviral therapy and the design of therapeutic regimens has been influenced by the following key findings from studies on the pathogenesis of HIV infection:

- demonstration that a continuous high-level of replication of HIV is present from the early stages of infection (at least 10^{10} particles are produced and destroyed each day)
- demonstration that a specific immune response to HIV occurs in HIV infected subjects during “primary” infection but begins to decline after the first months of infection.

The strength of this primary immune response may be predictive of subsequent concentrations of HIV in the body as measured by the plasma HIV-RNA or “viral load”.

- demonstration that the measured concentration of plasma viral load is predictive of the subsequent risk of disease progression and death.
- proof that combination antiretroviral therapy is not only able to consistently suppress HIV replication, but also able to induce a significant delay in progression to AIDS; this survival benefit is particularly marked in previously untreated patients.
- elucidation of the molecular, functional and clinical impact of resistance to antiretroviral drugs.



Since ongoing replication of HIV drives the disease process, causing progressive immunological damage, an ideal target of antiretroviral treatment is to obtain timely and sustained suppression of viral replication. Many ART regimens that achieve this target to some degree have already become available. Reliable techniques for quantifying HIV in plasma, measured as the amount of HIV-RNA or the “viral load” are also available and have allowed clinical researchers to compare the relative antiviral potency of various antiretroviral drug regimens, while providing a rational tool for monitoring the efficacy of ART in clinical practice. Measurement of the numbers of CD4+ cells in the blood are a reliable indicator of the extent of immunological damage caused by HIV infection and provide further rationale for clinical decisions on antiretroviral therapy.

While the progress so far has been impressive, there is a growing appreciation of some of the difficulties associated with ART and much work still remains to be done. Difficulties with adherence to treatment, long-term toxicity and cross-resistance among antiretroviral drugs have become major drawbacks of current ART strategies. Even with the most potent antiretroviral drug regimens available today, there exists a proportion of patients who fail to have complete and durable virologic responses to therapy for a myriad of reasons. These shortcomings of the current regimens are particularly evident in patients whose baseline levels of plasma “viral load” are high, who have had extensive prior treatment and in whom the stage of disease is advanced.

1.2. CHARACTERISTICS OF AVAILABLE ANTIRETROVIRAL DRUGS

Currently available antiretroviral drugs belong to two major classes:

1. Reverse Transcriptase Inhibitors (RTIs)
2. Protease Inhibitors (PIs).

Reverse Transcriptase Inhibitors are further divided into 2 groups:

- 1.1 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- 1.2 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs).

In most industrialised countries a range of antiretroviral agents have been approved, licensed and registered for the treatment of HIV. At present, they include:

six NRTIs

zidovudine (AZT, ZDV)
didanosine (ddI)
zalcitabine (ddC)
stavudine (d4T)
lamivudine (3TC)
abacavir (ABC)

three NNRTIs

nevirapine (NVP)
efavirenz (EFV)
delavirdine (DLV)

five PIs

saquinavir (SQV)
ritonavir (RTV)
indinavir (IDV)
nelfinavir (NFV)
amprenavir (APV)

All these drugs act by blocking the action of enzymes that are important for replication and functioning of HIV. Once HIV invades a macrophage or T-lymphocyte, the enzyme HIV *reverse transcriptase* initiates copying of the viral genetic code (RNA) into the genetic code of the infected host cells (DNA). After this, HIV genetic material is integrated into the host's DNA. This is



followed by multiplication, creating several billion new copies of HIV per day. The enzyme *protease* contributes to viral reproduction by enabling the assembly and release of viable particles of HIV from infected cells.

For optimal efficacy, antiretroviral drugs, usually from different classes, must be used in combination. A similar approach to therapy is already established practice in the treatment of other important long-term diseases such as cancers, tuberculosis and leprosy. Several combination regimens with demonstrated effectiveness in achieving durable suppression of HIV replication are available.

All available antiretroviral drugs have class-specific adverse effects, which are summarised below. For more details on drug specific adverse effects, see Annex II.

Nucleoside Reverse Transcriptase Inhibitors

(NRTIs) may cause fatty change in the liver, which is reversible upon stopping the medications, or lactic acidosis, a metabolic complication that is potentially fatal if unrecognised. These two adverse effects are due to toxicity of the NRTIs on cellular mitochondria. Changes in body fat distribution as well as derangements in the metabolism of fats, which are described below, have also been associated with the prolonged use of NRTI containing regimens.

Protease Inhibitors

(PIs) have been associated with body fat redistribution which manifests physically as thinning of the arms, legs and face and/or deposition of fat in the abdominal and shoulder regions. A further effect of this class of drugs on the metabolism of fat may result in raised levels of serum cholesterol and serum triglycerides, in

insulin resistance and rarely in increased blood sugar levels. The overall cumulative incidence of these metabolic disturbances may be 30% to 60% after 1 to 2 years of treatment, increasing with duration of therapy. All drugs in this class may cause bleeding episodes in patients with hemophilia.

Non-Nucleoside Reverse Transcriptase Inhibitors

All NNRTIs may cause a skin rash. These rashes are generally mild and self-limited, though severe forms similar to a Stevens-Johnson syndrome have been reported. NNRTIs may also cause elevation of serum aminotransferases and rare cases of fatal hepatitis have been reported.

1.3. INITIATION OF THERAPY

Earlier hopes that HIV could be eradicated from an infected individual were based on the erroneous assumption that complete suppression of viral replication could be achieved using currently available therapies. It is now known that low-level replication of HIV occurs at concentrations of plasma “viral load” below the limits of detection by the most sensitive assays in use. The decay half-life of resting memory CD4+ lymphocytes which harbor latent HIV in ‘sanctuary sites’ in the body, is at least 6 months and as long as 44 months. It is therefore estimated that eradication of HIV with ART alone would take at least a decade and so the goal of treatment must now be redirected towards the long-term management of a chronic infection.

The ultimate aim of antiretroviral treatment must be maximal suppression of HIV replication because the major short-term risk of any continuing viral replication in the presence of antiretroviral drugs, is the emergence of drug resistance. The success of ART is determined more by the patient's compliance with and adherence to the prescribed regimen than by the specific drug combination used. Decisions about when to start therapy and



what regimens to use are crucial because future treatment options may be severely compromised by an initial regimen that is inadequately adhered to or insufficiently potent. Physicians and patients together need to weigh the advantages and disadvantages of starting antiretroviral therapy and make individualised informed decisions.

Arguments in favour of early initiation of antiretroviral treatment include:

- HIV infection almost invariably causes progressive immune damage
- disruption of the immune system and the building of viral reservoirs are early events
- the natural history of untreated HIV infection includes selection for more diverse and more virulent strains of HIV

There is, however, an increasing tendency to defer initiation of ART until immune deficiency becomes measurable and the risk of disease progression becomes relevant because:

- the risk of disease progression is low until substantial CD4+ cell loss has occurred
- immune recovery is impressive even when therapy is delayed
- many patients only achieve incomplete or transient control of viral replication, resulting in selection for resistant strains of HIV
- any regimen has toxicity and cost.

According to current published international guidelines, the following broad criteria guide the selection of patients for initiation of therapy:

- all patients with symptomatic HIV infection, regardless of CD4+ count and “viral load” levels
- all patients with CD4+ counts below 350/mm³
- all patients with a high viral load (i.e. above 30,000 copies/ml by RT - PCR*)

Current guidelines recommend that treatment be **considered** for patients in the intermediate range, i.e. plasma viral load between 10, 000 and 30,000 copies/ml (RT-PCR) and CD4+ cell counts between 350/mm³ and 500/mm³.

Treatment of asymptomatic patients, with CD4+ cell counts above 500 mm³ is generally **deferred** as long as the probability of significant immune system damage and of clinical progression of HIV infection remains low.

1.3.1. Choice of regimen

Several regimens with acceptable antiviral potency are available, particularly for patients being treated for the first time. These regimens are composed of three to four drugs. Two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) generally form the backbone of most of these combinations. The choice of specific NRTI is based on convenience, adverse effects and patient preference.

Possible NRTI combinations (not in preferred order)

- zidovudine + didanosine, zalcitabine, or lamivudine
- stavudine + didanosine or lamivudine

Zidovudine and *Stavudine* should not be used together because of their antagonistic effect on each other. Similarly, *Didanosine* and *Zalcitabine* may lead to additive neurotoxicity and should not be combined.

* The different techniques used for measuring viral load; reverse transcriptase polymerase chain reaction (RT-PCR), branched chain DNA (bDNA) and nucleic- acid sequence based amplification (NASBA), produce different results that are consistent within the technique, but different between techniques. The values of viral load referred to in this document are those of RT-PCR.



Combination regimens containing a Protease Inhibitor

PI-containing regimens, (2 NRTIs + 1 PI), have been the first choice for initiating ART since 1997 and there is sufficient data on their effectiveness over the last two to three years. Protease Inhibitor regimens have proven potency and are effective in patients at all levels of plasma “viral load.” However, there are important disadvantages that limit the acceptability of PI containing regimens:

- complexity of the regimens makes adherence difficult
- cross-resistance between different PIs may limit future use if initial therapy fails
- there is growing concern over the long-term toxicity of PIs, particularly the fat redistribution and the metabolic abnormalities whose effect on cardiovascular morbidity and mortality remains uncertain.

Combinations of 2 PIs are increasingly being used instead of a single PI because they have pharmacokinetic advantages and possibly increase the PI regimen’s potency while potentially improving adherence to therapy. Addition of a reduced dose of *Ritonavir*, to *Saquinavir*, *Indinavir* or *Amprenavir* improves the pharmacokinetic profiles, may reduce pill burden, lower the dose frequency, lower cost, and obviate the need for administration of PIs on an empty stomach. The long-term benefit and toxicity of dual PI combinations remains to be fully characterised.

Combination regimens without a Protease Inhibitor

Combinations between NNRTIs and NRTIs have recently gained popularity. There is convincing evidence from controlled clinical trials that in treatment-naïve patients, NNRTI regimens offer a suitable alternative to PI-containing combinations in terms of antiviral potency. Besides the advantage

of deferring the introduction of PIs, NNRTI containing regimens may also allow for a lower pill burden and for improved adherence. The main disadvantage of NNRTIs is the ease and rapidity with which resistance develops to the individual drugs in this class if they are used in the context of a regimen that is not maximally suppressive and the very strong likelihood that cross class resistance will follow. Data on the long-term clinical efficacy of NNRTI containing regimens remains limited.

The use of three NRTIs to “spare” both PIs and NNRTIs has recently been proposed. Most data refer to the combination of *abacavir*, *zidovudine* and *lamivudine* which has shown durable antiviral activity (after 48 weeks of treatment), equivalent to that of a “standard” 2NRTI + 1PI regimen (*zidovudine/lamivudine/indinavir*), in treatment naïve patients. This combination, however, seems to have reduced potency in patients with high baseline plasma viral loads. The main attraction of a 3NRTI regimen is deferral of the use of PIs, while also sparing the NNRTI and placing only a single class of antiretroviral drugs “at risk” for the development of resistance. Once again, the long-term efficacy and toxicity of multinucleoside regimens remains unknown and there is concern over the potential possibility of selecting for multinucleoside-resistant variants of HIV.

There is no data at present demonstrating superiority of any one of the above acceptably potent initial regimens over the others and recommendations for a specific initial regimen or for a specific combination of individual drugs cannot be made. The choice of a particular regimen remains individualised with consideration given to the strength of supportive data, the tolerability of the regimen, the potential for adverse effects, likely drug-drug interactions,

**Table 1. Summary of currently available initial ART regimens***

Advantages	Disadvantages
2 NRTIs + 1 PI	
Solid clinical data Longest experience for viral suppression	Complexity and high pill burden May compromise future PI regimens Concerns on long-term toxicity
2 NRTIs + 2 PIs	
High potency Low pill burden	High pill burden with some regimens Long-term toxicities unknown
2 NRTIs + 1 NNRTI	
Low pill burden Equal potency to PI regimens	Limited long-term data Compromises future NNRTI regimens
3 NRTIs	
Defers 2 classes (PI, NNRTI) Low pill burden	Lower potency in patients with high baseline viral load Limited long-term data May compromise future NRTI regimens Potential convergence of mitochondrial toxicity

* Source: Carpenter et al. *JAMA*, January 19, 2000; 283 (3): 384.

convenience and likelihood of adherence and the potential for alternative treatment options should an initial combination fail.

1.4. MONITORING

Response to ART is monitored clinically and biologically. The most important biological measurements are the concentration of HIV – RNA in plasma (the “viral load”) and CD4+ cell counts. These measurements correlate with clinical outcome.

The desirable “virologic” endpoint is a plasma viral load that is “below the limits of detection”, by the most sensitive assay being used, within 3 to 4 months of starting treatment and the achievement of a minimum decline from the baseline viral load of 1.5-2.0_{log} by the end of the first month of treatment. In patients with higher baseline plasma viral loads (e.g. above 100,000

copies/ml by RT-PCR) maximal suppression of viral replication may take a longer time.

When optimal response to therapy is achieved, the median CD4+ cell rise is 100 – 200 cells within the first year. The CD4+ cell response may lag behind the “virologic” response in timing and at times the two responses may even be discordant.

The optimal frequency of viral load monitoring is unknown. In general, plasma viral load is checked within 1 month of initiating therapy and two-monthly thereafter until the virologic goal of therapy, i.e. viral load below the limits of detection, is achieved. Following this, plasma viral load may be checked every 3 to 4 months.

Due to possible individual oscillations in the concentrations of HIV1-RNA and to variability in

**Table 2a. HIV-RNA measurements in monitoring antiretroviral therapy**

HIV-RNA levels that suggest initiation of therapy	■ above 30,000 copies/ml by RT-PCR
Target level of HIV-RNA after initiation of treatment	■ “below the limits of detection” (at present taken as below 50 copies/ml RT-PCR) (< 400 copies/ml may be acceptable in some settings)
Timing of target response	■ “below the limits of detection” within 3 to 4 months of initiating ART (in patients with high baseline HIV-RNA levels, maximal suppression may not be for 6-8 months)
Frequency of HIV-RNA measurements	■ at baseline: 2 measurements 3-4 weeks apart ■ within 1 month of starting therapy to confirm antiviral activity of the regimen ■ every 2 months until viral load is below the limits of detection ■ every 3 to 4 months thereafter together with CD4 count (shorter intervals before critical decisions on therapy)

the assays in use, the baseline viral load measurement before initiation of treatment and any measurement thereafter that indicates a viral “rebound” significant enough to warrant considering a change in therapy, is routinely confirmed by a repeat test.

1.5. TREATMENT FAILURE

The most frequent reasons for changing treatment are drug toxicity, drug intolerance, difficulties with adherence to the regimen and treatment failure i. e. a drug regimen that is providing insufficient control of viral replication as indicated by lack of an adequate and sustained suppression of plasma HIV-RNA, lack of a satisfactory increase in CD4+ cell count or clinical progression of disease.

In clinical trials, a substantial proportion of patients (over 30%) do not achieve viral loads below the limits of detection. This is dependent on many factors such as baseline viral load and CD4+ count, primary acquisition of drug resistant virus, prior antiretroviral treatment, occurrence of adverse events and poor quality of adherence. In clinical practice, up to one year after the initiation of potent combination antiretroviral therapy, up to 1/3 of patients on ART may have viral loads above 20,000 copies/ml. (RT-PCR)

Table 2b. Viral load in treatment failure

Changes in HIV-RNA that suggest treatment failure

- insufficient viral suppression 4-6 months after starting ART
- confirmed return above 400 copies/ml (by RT-PCR) in a patient with previously undetectable viral load

Failure to reach the virologic target of therapy prompts

investigation into probable problems of drug adherence, drug absorption or the presence of drug resistant virus.

**Table 3. Cross resistance among available classes of antiretroviral drugs and possibilities of subsequent sequencing of drugs from the same class.**

	Likelihood of Cross-Resistance	Possibility of Sequencing	Comments
NNRTIs	High	No	may only have one chance
PIs	High/Moderate	Yes	Recommendations about optimal sequencing cannot be made from ART history alone
NRTIs	Moderate/Low	Yes	Cross resistance may be due to unique pathways of multi-drug resistance

The management of treatment failure depends on the reasons for failure. Where toxicity and intolerance are the main problems, supportive medication, dosage alteration or substitution of the offending drug is reasonable. When adherence difficulties are responsible for treatment failure, measures aimed at improving the patients' compliance are advised. If poor control of viral replication has been going on for an extended period of time, the presence of drug resistance is likely and resistance testing may, in this instance, guide the choice of subsequent treatment.

1.6. HIV RESISTANCE TO ANTIRETROVIRAL DRUGS

The high rate of replication that is found throughout the course of HIV infection and the variability of HIV, coupled with the relative inaccuracy of the enzyme HIV reverse transcriptase, are the main reasons for the frequent occurrence of copying errors in the transcription of viral genetic information. HIV replicates at the rate of around 10^8 to 10^{10} virus particles per day, probably giving rise daily to about 3×10^{-3} spontaneous changes (mutations) in its genetic sequence. The ultimate size of a viral population containing a mutation is probably determined by three concurrent factors: the forward mutation frequency, the replicative capability of the mutated virus and the "age" of the viral population containing the mutation i.e. how long ago this population was generated. With the on-going production of genetic variants of

HIV there is then a continuous selection for the "fittest" virus population.

Sub-optimal ART regimens that allow replication of HIV to continue in the presence of antiretroviral drugs, encourage the growth of viral populations that are carrying a genetic mutation which protects against these drugs. It is likely that many of these drug resistance mutations already exist before any antiretroviral drug is introduced and are further encouraged to proliferate under the selective pressure exerted by drug treatment.

Antiretroviral therapy can minimise the emergence of drug resistance in two ways:

- by maximising and sustaining the suppression of viral replication
- by using drugs where multiple mutations are required before resistance can occur.

In recent years laboratory testing for antiretroviral drug resistance has become available raising the possibility of using resistance testing to guide therapeutic choices. The testing methods in use, however, are still hampered by technical complexity, poor sensitivity, difficulties in interpretation and high cost. The place of resistance testing in every day clinical practice remains to be clearly defined because while it appears useful in patients experiencing treatment failure, its utility in



other situations (treatment naive patients, patients who have failed on multiple regimens or pregnant HIV-positive women) is still under investigation. When performing testing for antiretroviral drug resistance, it is important to ensure that this is done while the patient is still on therapy in order to maximise accuracy.

Cross resistance among the available classes of antiretroviral drugs is common and is an important consideration when assessing the possibility of **sequencing** (replacing one drug with another) should it become necessary to change a therapeutic regimen (Table 3). Cross-resistance implies that a population of virus resistant to one drug in a class is also resistant to other drugs of the same class. This is particularly liable to occur with the NNRTIs especially if they are used as part of a regimen that produces incomplete suppression of viral replication. The NNRTIs in general present a very low "genetic barrier" to resistance because a single mutation is sufficient to produce resistance.

PIs and NRTIs are more robust in this respect since multiple mutations are required to confer resistance to drugs in these classes.

1.7. FUTURE APPROACHES TO THERAPY

The seemingly large number of possible antiretroviral drug combinations is only apparent. Therapeutic options are actually limited by cross reactivity within the currently available classes of antiretroviral drugs. New drugs with increased potency that are safer, easier to take, with more favourable pharmacologic properties and with activity against drug-resistant viruses, are needed. Validation of drug resistance testing for use in clinical practice will provide clinicians with a helpful patient management tool and the choice of therapy will hopefully be guided by individual

resistance profiles, allowing for more effective treatment.

It is becoming increasingly evident that the course and the outcome of HIV infection are mostly determined by events that take place during primary infection. Future treatment strategies, through controlled studies, will focus on the early recognition and treatment of primary HIV infection.

There is evidence that a specific and effective cellular immune response to HIV occurs in infected subjects. This has led to the exploration of alternative approaches to therapy that would aim at enhancing this host immune response such as therapy with drugs like Interleukin 2 and with certain HIV-derived immunogens. Studies are ongoing to design further strategies of treatment based on immunologic intervention.

The example of the "long term non-progressor" (individuals whose HIV infection is effectively controlled by their own specific CD4+ T cell response) suggests that enhancing the immune response may lead to a stable equilibrium between virus and host. A similar response is observed in other persistent viral infections such as those caused by herpesviruses, where the host's immune system is able to keep a virus silent. One approach to ART that is under investigation is antiretroviral therapy with structured treatment interruptions. The hope is that intermittent interruptions in ART, by allowing host immunity to be exposed to HIV, may act to augment the duration and the strength of host immune responses to HIV and therefore increase immunologic control of the infection. Additional potential advantages of structured interruptions of ART are: reduced toxicity, improved tolerance, greater adherence to treatment and reduced overall cost. Results from a few uncontrolled studies are available which



indicate that the majority of patients seem to experience a rapid rebound in plasma HIV-RNA during treatment interruptions as well as a rapid decline in CD 4+ cell counts. The implications of these results and the possibility of boosting HIV-specific immune responses through this approach still remain controversial and need to be further clarified by controlled studies.

A variety of other approaches to stimulating the immune system are under investigation. While research into eradication of HIV also continues, a combination of potent ART with immune-based therapies may be the most durable approach to achieving long term containment of HIV replication.



SECTION TWO SOME EXPERIENCES WITH ART IN RESOURCE LIMITED SETTINGS

Experiences with ART in resource limited settings are a source of important information in terms of defining the standards of clinical practice in those settings as well as the social and economic contexts which influence the use of antiretroviral drugs. National programmes and pilot initiatives from six low and middle-income countries are described in the pages that follow. All have in varying ways fulfilled the essential pre-conditions (See section 3.1) for introduction of ART programmes.

2.1. ART COVERAGE

The proportion of people with symptomatic HIV infection who are receiving ART ranges from small to insignificant. In Uganda, probably less than 1% of people with HIV related illnesses are receiving ART. In Thailand, in 1996, nearly 10% of people eligible for treatment were being treated through the Ministry of Public Health (MOPH) programme in 58 hospitals, but that proportion has substantially decreased since then. In Brazil, however, nearly 100,000 out of 530,000 people with HIV infection are receiving ART following a presidential decree, in November 1996, that access to antiretroviral drugs be made universally available through the public health system.

2.2. CONTEXT: PUBLIC OR PRIVATE SECTOR, DONOR SUPPORTED AND RESEARCH PROJECTS

With some exceptions such as Brazil, where ART is provided at no cost within the public health sector, “ability to pay” is determining access to drugs in many low and middle-income countries. The drugs themselves may be obtained privately

and medical care as well as related services such as laboratory monitoring is often provided through the private sector. The public/private distinction is however blurred by the fact that private patients who can pay for the drugs are often treated and monitored in “centres of excellence” (e.g. the teaching hospitals of major cities) which themselves are publicly funded. A few patients receive drugs at subsidised cost through donor supported projects such as the UNAIDS Drug Access Initiative in Ivory Coast. Similarly, in Senegal, less than one hundred patients are being treated with antiretroviral drugs, through an initiative supported by the National Aids Control Programme, Agence Nationale de Recherche sur le SIDA – France, Institut de Médecine et d’Epidemiologie Africaine – Paris and Fondation d’Espoir – France.

A minority of PLHA receive free treatment through participation in clinical trials which may be externally and/or nationally funded. This is the case in Thailand, where patients are receiving drugs through the HIV-NAT clinical trials conducted in 19 hospitals around the country.

2.3. QUALITY OF CARE AND OUTCOMES

Available data suggest that the clinical outcomes of treatment, in the context of centres of excellence, externally funded projects or clinical trials, are very similar to those in industrialised countries. From about 1997, HIV care centres in 2 large Brazilian cities have recorded a significant decrease in the number of AIDS deaths, a reduction in the prevalence of major HIV related opportunistic



infections and an overall decrease in the number of hospitalisations for HIV related illnesses. In the context of unregulated practice, the quality of care and the outcomes of treatment may be different but because such situations are difficult to evaluate, there is no information available.

2.4. LABORATORY MONITORING SERVICES

Access to reliable laboratory monitoring is limited in low and middle-income countries and is concentrated in the major cities. Within the public health system in Brazil, there is a network of 70 laboratories with capacity to perform CD4+ counts and 56 laboratories with the capacity to measure plasma viral load.

Elsewhere, the necessity for regular CD4+ cell counts and estimations of plasma viral load to evaluate the effectiveness of treatment adds to the overall cost of ART and within the private sector, laboratory monitoring is largely dependent on financial resources, so that patients themselves will often request for less monitoring in order to pay for more drugs. Treatment centres accredited to the UNAIDS HIV Drug Access Initiative in Uganda, have been able to carry out the required virologic monitoring of ART through the collaboration and aid of a donor funded research laboratory, which provides the tests at no cost to patients, as part of the evaluation of that pilot initiative. Similarly, laboratory monitoring has been provided at no cost to patients within the Drug Access Initiative in Ivory Coast, while in Thailand, regular immunologic and virologic monitoring form part of the research protocols for clinical trials.

2.5. SURVEILLANCE FOR DRUG RESISTANCE

Monitoring for resistance is rarely undertaken in any developing country setting but its importance as a public health responsibility is recognised. Within every ART programme, as for any antimicrobial treatment, lies a public health

responsibility to protect the future utilisation of the drugs by minimising the emergence of drug resistance. Modalities for surveillance of HIV drug resistance are a necessity and though the technology is too costly for most resource limited countries to afford, there exist innovative ways to strike a balance between resource constraints and good clinical/public health practice. To this end, Ivory Coast, Senegal and Uganda have initiated collaboration with international laboratories that have the capacity to carry out monitoring for antiretroviral drug resistance.

2.6. SUPPLY AND DISTRIBUTION OF THE DRUGS

By and large, the entire range of antiretroviral drugs is available anywhere in the world through private channels. Where resources permit, the supply may be adequate and consistent. Through the public sector, however, and for low-income patients, the choice of drugs may be somewhat restricted. This has implications for decisions such as when to start therapy, which therapeutic regimens to use, and what to do when treatment fails. In the context of clinical trials, reliability of supply and quality of drugs is relatively well assured. In the donor-supported projects, despite the subsidised cost of antiretroviral drugs, it is still not unusual for financial constraints to lead to cessation of treatment. In Brazil, a substantial and rapidly increasing proportion of antiretroviral drugs are being produced in the country with considerable cost savings and a positive impact on sustainability of supply.

2.7. INITIATION OF TREATMENT

The majority of patients in low income countries start treatment at an advanced stage of HIV disease as illustrated by records from some of the treatment centres: in one treatment centre in Ivory Coast, 55% of patients were in CDC category 3 (advanced disease) at the start of treatment, in Senegal this



proportion was 75%, while 68% of the patients at the Mildmay centre in Uganda had advanced disease at the start of therapy. This is due to a combination of factors such as late care seeking through fear or denial, a lack of accessible counselling and testing services so that many people are unaware of their HIV infection and the high cost of the drugs which leads to treatment being deferred.

Initiation of treatment for private patients may follow the same criteria as established in industrialised countries. At the same time, private sector patients are often advised to save scarce resources and delay initiation of ART until the occurrence of the first serious HIV related illness. In the context of clinical trials and donor-supported projects, treatment is initiated according to biological criteria determined by in-country technical committees. In Senegal, treatment for symptomatic patients is started when the CD4+ cell count is below 350/mm³ and the viral load above 10,000 copies/ml, while the eligibility criterion for asymptomatic patients is a viral load above 100,000 copies/ml. In the public health system in Brazil, the recommendation is

that PLHA be treated when CD4+ cell count is between 200 and 350 cells/mm³ or if the viral load is over 50,000-copies/ml.

2.8. CHOICE OF THERAPEUTIC REGIMEN

Most of the ART initiatives particularly those linked to clinical trials and in the externally funded projects have aimed to use the highly potent three-drug combination therapies i.e. regimens containing a Protease Inhibitor, as recommended by international guidelines. In Brazil, 55% of patients on ART are on triple combination therapy as are 43 of 109 patients treated in one centre in Ivory Coast. Generally speaking, however, as the choice and sustainability of ART regimens is largely determined by cost, there is widespread use, especially in private practice, of dual nucleoside regimens (2 NRTIs) because of simpler monitoring requirements, improved compliance and lower cost. There is also a significant amount of use of Hydroxyurea containing regimens. The implications of these therapeutic practices seeking to adapt ART combination regimens to the resources of low-income countries are discussed in section 3.4.



SECTION THREE GUIDE TO ART IN RESOURCE LIMITED SETTINGS

3.1. WHAT SHOULD BE IN PLACE BEFORE INITIATING ART PROGRAMMES*

Due to the high cost of antiretroviral drugs, the complexity of the regimens and the need for careful monitoring, specific services and facilities must be in place before considering the introduction of ART into any setting.

The following conditions are essential to the introduction of ART:

- Assured access to voluntary HIV counselling and testing (VCT) and institution of follow up counselling services for ART to ensure continued psychosocial support and to enhance adherence to treatment.
- Capacity to recognise and appropriately manage common HIV related illnesses and opportunistic infections.
- Reliable laboratory monitoring services including routine haematological and biochemical tests for the detection of drug toxicity as well as access to facilities for monitoring the immunologic and virologic parameters of HIV infection.
- Assurance of an adequate supply of quality drugs, including drugs for the treatment of opportunistic infections and other HIV related illnesses.

* **ARV Treatments: Planning and Integration into Health Services** – Guidance Module number 3, Guidance Modules on Antiretroviral Treatments. WHO/ASD/98.1; UNAIDS/98.7

- Identification of sufficient resources to pay for treatments on a long-term basis.
- Information and training on safe and effective use of antiretroviral drugs for health professionals in a position to prescribe ART.
- Establishment of reliable regulatory mechanisms against misuse and misappropriation of antiretroviral drugs.

3.2. COUNSELLING FOR ART

ART may be a lifelong undertaking. A relationship of confidence needs to be established from the outset between the patient and the care team. It is important that adequate time is set aside for counselling so that appropriate and informed decisions on therapy and its implications are made by the patient, based on information given to them that is as accurate and as complete as possible. Many people seeking ART will have had prior counselling at the time of diagnosis (pre & post-test counselling). The positive messages and future plans initiated during pre and post-test counselling should be reinforced during counselling for ART.

ART must not detract from HIV prevention messages. Even though the aim of treatment is to lower the amount of HIV in the blood, often to levels below the limits of detection by sensitive laboratory assays, patients must not conclude that it is no longer necessary to use protective measures to prevent the transmission of HIV. Counsellors should stress that HIV can still be transmitted even while on ART.



Whenever available, the services of a care provider with counselling skills are invaluable. However, the counselling and psychosocial support process is an ongoing component of ART requiring contributions from the prescribing physician, the pharmacist, other health workers, family members and peer support groups of PLHA. An assessment of psychosocial support needs should be made right from the start with the intention of assuring that this will be maintained through out the period of therapy.

The issues that need to be addressed during counselling may be broadly classified into 5 categories: Financial considerations, Drug information, Emotional support, Issues of disclosure and Adherence.

3.2.1. FINANCIAL CONSIDERATIONS

In many developing countries the patient or their family meets the cost of ART. Alternatively, drugs may be obtained as part of a clinical trial; as part of an “expanded access” program; through private sector funding, e.g. employment health insurance; or as a donation. It is important to discuss how the drugs are going to be paid for before embarking on treatment since financial constraints are a common reason for default from treatment. The importance of adherence to therapy and the consequences of intermittent therapy, cessation of therapy or of taking sub-optimal doses to minimise drug costs, should be candidly discussed with all concerned.

3.2.2. DRUG INFORMATION

Antiretroviral drugs have received a large amount of publicisation in the popular press. Even in low-income countries many people with HIV know about antiretroviral drugs and may at times have unrealistic expectations about the availability and effects of ART. Counsellors should be equipped to

answer questions on the different ART drug regimens, the requirements for clinical monitoring of ART, the expected results, the possibility of treatment failure and the criteria for changing or cessation of therapy. Sources of reliable medical information on ART which are patient oriented, should be identified and provided.

The counsellor must inform that ART is not a cure. Elimination of HIV from the body has not been achieved using the most potent antiretroviral combination therapies available and even when HIV viral RNA is not detectable in the plasma, there is still ongoing viral replication. The drugs will therefore need to be taken for an indefinite period of time. It is equally important to convey an understanding that knowledge on ART is still evolving and that up to date information about the positive and the possible negative outcomes of treatment will constantly be provided.

Some adverse effects such as headache, nausea and minor allergic reactions are common in the first few weeks of ART. Counsellors should be aware of these and reassure clients that some initial adverse effects will usually lessen with time while simple symptomatic remedies can alleviate many of them. The nausea and vomiting that is commonly experienced at the onset of treatment with zidovudine, for example should not lead to discouragement or discontinuation of treatment. Counsellors should at the same time give detailed information on the possibility of potentially serious adverse effects in the event of which drug therapy must be discontinued. Examples are the polyneuritis and hepatitis, which can occur with Reverse Transcriptase Inhibitors and the skin rash that results from a severe hypersensitivity reaction to abacavir. Patients need to know how to recognise the symptoms of these adverse effects and where to go for help should they occur.



The presence and types of food in the stomach affects the absorption of some of the Protease Inhibitors. Dietary changes will have to be made and meals will often have to be planned carefully around a drug regimen. This can be inconvenient and disrupt family and social life. If family members can be involved in discussions about these issues, it will help them to understand the importance of timing meals and changing routines. The counsellor may have to take time to work out a “meal and drug taking time table” that fits in with the client’s and the family’s life style. Many PLHA may resent the constraints that taking drugs imposes on their lives and this has to be acknowledged and explored when starting therapy. Asymptomatic PLHA who feel unable to embark on the strict regime that some regimens will impose on them may do better to postpone treatment and the implications of this advice should also be discussed.

3.2.3. EMOTIONAL SUPPORT AND DIFFICULT DECISIONS

Many PLHA commencing ART in developing countries, experience feelings of guilt, fear, anxiety and isolation because this therapy is extremely costly and not universally available. Many may have partners and/or children who also require treatment and who cannot access it for financial reasons and vital family resources may be being diverted to buy the medications. Patients often know and associate with other PLHA who themselves are not being treated but who were a source of encouragement and support before the decision to commence ART. Very often patients themselves question the wisdom of commencing antiretroviral therapy at all. Time taken to work through these feelings and doubts will significantly enhance commitment to therapy.

ART in symptomatic patients often results in remarkable clinical improvement. This

improvement however, is not universal. Furthermore, clinical improvement may be incomplete or short lived particularly in patients who have had prior antiretroviral treatment or when drug resistance or severe adverse effects supervene. Additionally, in many resource-limited settings, treatment is often put off until such advanced stages of immune deficiency that the outcome is less favourable. Counsellors will have to support patients through the disappointment of treatment failure and balance optimism and realistic caution. Depression and despair are common when CD4+ counts do not rise and weight is not gained as had been expected. This is aggravated when the patient is aware of draining his or her financial resources into a treatment that may be viewed as futile. There will also come a time when counsellor and patient will have to discuss cessation of treatment and end of life issues.

3.2.4. CONFIDENTIALITY AND SHARING HIV STATUS*

The disruption of life style brought about by complicated lifelong ART regimens should not be underestimated. Involving a partner or significant other in treatment counselling will make taking antiretroviral drugs much simpler. The counsellor should encourage disclosure of HIV status to partners and/or close relatives so that the burden of the drug-taking schedule can be understood and shared. Informing sexual partners of the continuing risk of HIV transmission, even while on ART, also ensures that protective action is maintained. It is however, important to explore the patient’s own perception of the risks associated with disclosure so that reassurance and support can be planned against such barriers to disclosure as the fear of rejection, abandonment and violence; the risk of losing one’s employment or the refusal of insurance. Antiretroviral treatment of children presents a special challenge for counselling on disclosure. Should children be told



about their own serostatus? Should their siblings be told? Should the school be told?

3.2.5. ADHERENCE TECHNIQUES

Incomplete adherence to the prescribed drug regimen is a major factor that limits the effectiveness of ART. The drug regimens are complex and the duration of treatment indefinite. In order to maximise the benefits of treatment immense personal discipline and commitment are required of the patient. Possible barriers to adherence such as number and timing of doses, number and size of pills, food restrictions and fear of undesirable side effects, should be identified and used to design programs to support adherence. A “drug timetable” is useful and helps patients with their drug-taking schedule. Reassurance concerning the immediate and long-term side effects of the drugs is also very helpful and enhances adherence. In addition, the patient should be given explanations on the variety of alternatives available in the event that an initial drug regimen becomes intolerable.

3.3. CLINICAL EVALUATION BEFORE INITIATION OF ART

A detailed clinical evaluation is essential prior to initiating ART and should aim to:

- assess the clinical staging of HIV infection
- identify past HIV related illnesses

* Further reading:

1. **Counselling for HIV/AIDS A key to caring.** WHO/GPA/HCS/95.15.
2. **The Implications of Antiretroviral Treatments.** Informal Consultation – April 1997. WHO/ASD/97.2.
3. **Safe and Effective Use of Antiretroviral Treatments.** Guidance Module 4; Guidance Modules on Antiretroviral Treatments. WHO/ASD/98.1; UNAIDS/98.7.
4. **Ethical and Societal Issues Relating to Antiretroviral Treatments.** Guidance Module 9; Guidance Modules on Antiretroviral Treatments. WHO/ASD/98.1; UNAIDS/98.7.
5. **HIV/AIDS and Human Rights** – International guidelines. OHCHR/UNAIDS; HR/PUB/98/1.

- identify current HIV related illnesses that will require treatment
- identify co-existing medical conditions that may influence the choice of therapy

The standard detailed medical history should include questions on the following:

- when the diagnosis of HIV infection was first established
- the current symptoms and concerns of the patient
- symptoms of all past illnesses and if known the diagnosis and treatment given
- a history of symptoms of or previous treatment for tuberculosis
- a history of possible contact with tuberculosis
- past symptoms of sexually transmitted infections
- the possibility of pregnancy in a woman
- social habits and sexual history

The following are important components of the physical examination:

- patient’s weight
- skin and lymphnodes:
 - herpes zoster, Kaposi’s sarcoma, lymphadenitis, HIV dermatitis
- oropharyngeal mucosa
 - candidiasis, Kaposi’s sarcoma, leucoplakia
- examination of the heart and lungs including examination of a Chest x-ray
- examination of the abdominal system particularly for liver and spleen size
- examination of neurological and musculoskeletal systems for:
 - mental state, motor or sensory deficits.
- whenever possible examine the optic fundus
 - retinitis or papilloedema
- examination of the genital tract

**Table 4. Initial laboratory evaluation for ART**

Essential lab investigations	Desirable investigations	Supplementary investigations that may be indicated by symptoms and signs
HIV Serology	HIV – 1 RNA	Histology on skin biopsy/lymph nodes
CD4+ counts or Total lymphocyte count		Screening for STIs
Complete Blood Count		Pregnancy test
Tests of Liver Function		Abdominal ultrasonography
Complete Urinalysis		
Chest X-ray		

The initial laboratory evaluation should provide the following:

- confirmation of diagnosis of HIV infection
 - HIV testing should be done or repeated, particularly where no prior documentation is available and especially if the patient is asymptomatic
- indicators of the patients immune status
 - CD4+ cell counts* are good indicators of immune function in HIV infection.
 - The total lymphocyte count correlates very well with CD4 cell counts, particularly in advanced HIV disease, and can be used as an indicator of immune function.
- information on the patients baseline haematological, hepatic and renal function
 - The baseline blood count complete with examination of a peripheral blood film is necessary because of the frequent occurrence of anaemia, neutropenia and thrombocytopenia both as complications of HIV infection and as adverse effects of ART.
 - Biochemical tests of liver function are needed to exclude co-existing hepatitis and as baseline references in case of ART drug induced hepatic toxicity. A complete urine analysis comprised of a test for glycosuria, proteinuria and careful microscopy of the urine sediment is adequate initial screening for baseline renal function.

- screening for tuberculosis
 - Tuberculosis is the most common OI in HIV infection in developing countries and must be actively excluded and/or treated. Examination of a chest X-ray is therefore considered an essential part of initial clinical evaluation.
- diagnosis of other intercurrent illnesses
 - Several “supplementary” laboratory investigations, for the diagnosis of HIV related or other illnesses that may require treatment, will be indicated by findings from the patient’s history and physical examination. Examples are histological examination of skin lesions to confirm Kaposi’s Sarcoma, aspiration or biopsy of enlarged lymph nodes and screening tests for sexually transmitted infections (STIs). This list is by no means exhaustive.

3.3.1. HIV-RNA TESTING

Plasma HIV-1 RNA assays/viral load assays are useful for indicating the prognosis of HIV infection, for indicating when asymptomatic patients should be treated and as a reference for subsequent monitoring of the virological response to therapy. In settings where resources are limited the availability and the cost of these assays are important considerations for the patient. Though desirable, there is no need to routinely perform a

* A number of alternative techniques to the conventional cytofluorometry method of measuring CD4+ cells should be available soon and these will allow for reduction in the cost of CD4+ cell measurements.



viral load assay as part of the initial laboratory evaluation of a patient who is symptomatic.

Some of the first generation viral load assays give falsely low results of viral load on samples from patients with subtype A/E infections and do not detect HIV-1 group O or HIV-2 RNA. The relative regional prevalence of HIV subtypes should therefore be taken into consideration when recommending viral load assays.

3.4. INITIATION OF THERAPY

3.4.1. WHOM TO TREAT

Most countries with ART programmes have established criteria for initiating ART developed by national technical committees, which balance the need to extend access to treatment as widely as possible against the feasibility of ART.

Wherever possible national criteria should be developed by countries themselves.

In resource limited settings, where the conditions necessary for the introduction of ART have been fulfilled, priority for treatment should be given to symptomatic patients with severe immune damage (i.e. CD 4 count below 200 cells/mm³), because these patients are at a high risk for disease progression.

In the event that initial viral load testing is available, patients identified to have very high plasma viral loads, (i.e. above 100 000 copies/ml RT-PCR) have a poor prognosis and should also be offered treatment.

3.4.2. CHOICE OF THE REGIMEN

The use of combinations of antiretroviral agents aimed at maximal suppression of viral replication is the standard of care. (see Table 1)

No currently available antiretroviral agent is sufficiently potent to provide sustained suppression of viral replication on its own. At best, monotherapy yields incomplete viral suppression for a very limited duration of time: 0.6 to 0.8_{log} reduction in the viral load for 6 to 8 months. Thereafter, drug resistance is inevitable and cross-resistance to other antiretroviral agents may emerge. Monotherapy is therefore not recommended for the treatment of HIV infection. However, for the specific indication of prevention of mother to child transmission of HIV infection, short course monotherapy is still recommended.

Dual Nucleoside Therapy (2 NRTIs)

Historically, controlled clinical trials comparing dual nucleoside regimens of 2 NRTIs to monotherapy demonstrated enhanced ‘virologic’ efficacy as well as a survival benefit, in patients with advanced HIV infection (CD4 counts below 350 cells/mm³).

Therapy with 2 NRTIs can potentially achieve a 1.5_{log} reduction in “viral load”.

Between 1995 and 1997, before the potent three-drug combinations became the standard of treatment, many PLHA were treated with dual nucleoside regimens. A small proportion of patients in industrialised countries are today still maintained on 2 NRTIs because this regimen is relatively well tolerated by the patients and careful clinical monitoring indicates continuing suppression of viral replication. It should nevertheless be noted that during the ‘era’ of dual nucleoside therapy in industrialised countries, despite some benefits on an individual level, there was no record of a significant beneficial impact at population level in terms of reduction in HIV related mortality.

**Table 5. Advantages and disadvantages of dual nucleoside regimens**

Advantages of 2 NRTI	Disadvantages of 2 NRTI
low cost	lower antiviral potency
lower pill burden/better tolerance	emergence of resistance more likely
easier to monitor	

Experiences from the resource limited countries where dual nucleoside regimens are presently being used indicate that there is some benefit from dual nucleoside regimens, but that these regimens do not achieve or sustain suppression of HIV replication to the same extent as the three-drug regimens.

Despite the limitations of dual nucleoside regimens, where a more potent regimen is not available: 2NRTIs may be suitable for treating patients with advanced HIV disease, who are at high risk for disease progression (e.g. CD4 count below 200 cells/mm³).

Patients with advanced immune suppression often have high levels of HIV activity as measured by the plasma viral load. Because of the limited duration of the clinical and immunological benefits of dual nucleoside therapy and because viral replication is very likely to continue during dual nucleoside therapy, every effort should be made to switch the patient to a maximally suppressive regimen in order to minimise the progressive accumulation of drug resistance mutations.

The place of Hydroxyurea

In many resource limited settings, Hydroxyurea + Didanosine or Hydroxyurea + Stavudine are occasionally used in the treatment of HIV because of the low cost of these combinations. Hydroxyurea has no direct antiretroviral activity and is not considered as an antiretroviral drug. Hydroxyurea may, however, enhance the antiviral activity of nucleoside

analogue reverse transcriptase inhibitors (NRTIs) through various possible mechanisms:

- depletion of host cellular enzymes that are essential for cell replication;
- repletion of cellular enzymes necessary for metabolising NRTI's to active form;
- depletion of numbers of activated lymphocytes vulnerable to HIV infection.

This specific targeting of host rather than viral proteins provides an alternative approach to antiretroviral therapy so that efficacy of hydroxyurea is not affected by emergence of HIV mutations resistant to NRTIs. The main disadvantage is that these effects are also exerted on other replicating cells in the host and this is the basis for the common toxic effects of hydroxyurea i.e. reduction in the numbers of circulating blood cells. The slight increase in antiviral efficacy when hydroxyurea is added to *Didanosine* or *Stavudine* is therefore offset by a significant decrease in the CD4+ cell numbers. This effect can be harmful in patients with low CD4 counts who also have active opportunistic infections. There have also been recent reports of fatal acute liver insufficiency as well as pancreatic insufficiency among patients receiving a Hydroxyurea + *Didanosine* regimen.

Much of the evidence for the therapeutic effectiveness of Hydroxyurea combined with *Didanosine* and/or *Stavudine* comes from small studies with short follow-up periods. Before any recommendation can be given, further safety and efficacy data are needed.

**Table 6. Laboratory monitoring for tolerance of ART**

Laboratory Tests	Antiretroviral drug class		
	NRTI	NNRTI	Protease inhibitor
Essential to monitor routinely and at baseline:			
Complete blood count	✓		
Urine (glucose, protein, microscopy)	✓		✓
Necessary when indicated by clinical features:			
Serum transaminases	✓	✓	✓
Serum amylase	✓		
Serum creatinine/Urea	✓		✓
Creatine phosphokinase	✓		
Serum triglycerides			✓
Blood glucose			✓

3.5. MONITORING ANTIRETROVIRAL THERAPY*

Patient on ART should be closely followed to assess adherence to therapy as well as tolerance of the treatment and efficacy of the treatment. At the start of treatment it is advisable for patients to be seen monthly and once stabilised they can then be seen every three to four months. More frequent visits may certainly be dictated by various intercurrent needs so follow up plans should be tailored to individual patient requirements.

3.5.1. Monitoring adherence to ART

PLHA from resource poor countries have identified the following as important determinants of adherence to ART:

- the quality of initial and continuing counselling resulting in well-informed decisions and commitment by the patient to start and to maintain ART.
- the availability of accessible, knowledgeable and committed medical support teams.
- the assurance of a continued supply of antiretroviral medications

* Further Reading: **Laboratory Requirements for the Safe and Effective Use of Antiretrovirals.** Guidance Module number 5. Guidance Modules on Antiretroviral Treatments. WHO/UNAIDS. WHO/ASD/98.1; UNAIDS/98.7

At each follow up visit, adherence to the treatment should be discussed in depth.

The “drug timetable” which was made at the onset of ART should be revisited to see how this is functioning in real life and the patient should be assisted to work through any difficulties they have encountered. Close co-operation and communication between clinicians, pharmacists/dispensers, other counsellors, patients and family are vital. Carers need to remain aware of the issues surrounding individual patients' access to ART in order to anticipate difficulties in adherence and to plan support.

3.5.2. Monitoring tolerance to ART

The causes of any new symptoms or signs developing after the initiation of ART should be identified whenever possible. New symptoms may be related to intercurrent illness or due to adverse effects of antiretroviral drugs. Shortly after commencing ART, certain opportunistic infections may become clinically apparent as a result of the syndrome of immune reactivation, and these should be diagnosed and treated.



If new complaints are due to adverse effects of drugs, these should be explained to the patient and appropriate measures implemented, be this by adapting the drug regimen, providing symptomatic treatment or giving simple reassurance.

Direct questioning on early symptoms of the documented clinically serious adverse effects of antiretroviral drugs is mandatory, as is systematic physical and laboratory examination to look for indicative signs. In this way adverse effects like severe anaemia and neutropenia; polyneuritis; pancreatitis; hepatitis; nephrolithiasis and serious hypersensitivity dermatitis can be detected early and remedial actions taken.

Table 6 lists the ancillary laboratory tests that should complement patient interview and physical examination to monitor for drug toxicity. The necessity for these tests will vary according to the antiretroviral drugs being used and to whether or not tests are indicated by the patient's symptoms.

3.5.3. Monitoring the efficacy of ART

The efficacy of ART is indicated by clinical improvement of the patient and by a favourable response of the biological markers of HIV infection, namely CD4+ cell counts and plasma "viral load".

Some clinical indicators of disease progression and response to treatment:

- a gain in body weight
- increase in total lymphocyte count
- decrease in frequency/severity of opportunistic infections
- decrease in occurrence/severity of HIV related malignancies

CD4 lymphocyte counts*

The clinical manifestations of HIV infection are mostly dependent on the levels of CD 4+ cells; the CD4 count. Where viral load assays are not available, a rise in the CD4 count is an acceptable indication of treatment efficacy. In addition, CD4+ cell levels are very useful when deciding on the time to start or to stop prophylaxis against certain opportunistic infections. In patients in whom undetectable viral load levels have been achieved, which indicates the desired suppression of retroviral activity, a median increase in CD4+ cells of about 100-200 cells per year may be expected. The magnitude of this increase in CD4+ cells will depend on the baseline CD4 count as well as other factors which influence the outcome of ART. It is worth noting that following initiation of therapy, the "CD4 response" as evidenced by rising CD4+ cell counts, is much slower than the "viral load response" and may take several months to years to be complete. A reasonable frequency of CD4 count measurements in patients on ART is every 3-6 months.

Plasma HIV-1 RNA assay or "viral load"*

The plasma viral load is a measure of HIV replication and the suppression of viral replication is one of the primary goals of antiretroviral therapy. Sustained suppression of HIV replication is not only an indication of the efficacy of treatment but also may delay or prevent the emergence of drug resistance. It is advisable to measure viral load shortly after initiating ART i.e. within 1 to 3 months, as a check on the effectiveness of the therapy. It also becomes necessary to measure the viral load when the response to therapy, as shown by the other indicators, is unfavourable and whenever a change in the therapeutic regimen is contemplated.

* Further Reading: **Laboratory Requirements for the Safe and Effective Use of Antiretrovirals.** Guidance Module number 5. Guidance Modules on Antiretroviral Treatments. WHO/UNAIDS. WHO/ASD/98.1; UNAIDS/98.7



When interpreting the results of viral load assays caution is advised for several reasons:

- viral load levels vary according to the technique that has been used, the laboratory where the test has been done, the time and the way the sample was transferred to the laboratory.
- viral load levels may be increased after a recent infection, vaccination or lapse in treatment;
- certain viral strains that are particularly frequent in developing countries may be difficult to detect with some of the commercially available testing methods.

Wherever ART is introduced, a reliable reference laboratory, where the necessary biological monitoring tests can be assured, should be established.

3.6. CONSIDERATIONS OF DRUG INTERACTIONS

The majority of patients presenting for care in resource limited countries have symptomatic HIV infection and so, in addition to antiretroviral agents, they are likely to be taking other medications:

- for the control of HIV/AIDS related symptoms
- for prophylaxis of opportunistic infections
- for treatment of opportunistic infections and tumours
- for treatment of other coincident infections

Successful ART results in amelioration of many HIV/AIDS related symptoms and a decreased likelihood of opportunistic infections. It may even be possible, once immune competence has been restored, to discontinue primary prophylaxis for some of the opportunistic infections. There are nevertheless, numerous possibilities for drug

interactions of which clinicians need to be aware. Drug interactions are of clinical importance if they increase the likelihood of drug toxicity or if they decrease the therapeutic effectiveness of an administered drug. The longer the duration of any drug therapy, the more significant this becomes. In the context of ART clinically important interactions are likely:

- between the different antiretroviral drugs that are prescribed
- between prescribed drugs and alternative or non-prescription medications,
- between drugs and food (see section 3.2.2)
- with certain "recreational" drugs

A detailed synopsis of all possible drug interactions is beyond the scope of this publication and only a few important examples are cited on the following pages.

There exist several sources of information on potential drug interactions, particularly where access to the Internet is available and these are well worth referring to.*

3.6.1. ANTIRETROVIRAL DRUGS AND THE TREATMENT OF TUBERCULOSIS

The Rifamycin antibiotics (Rifampin & Rifabutin) stimulate the activity of the enzyme system in the liver (cytochrome P450) that metabolises Protease Inhibitors (PIs) and Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). This can lead to a reduction in the blood levels of the PIs and the NNRTIs. Conversely, PIs and NNRTIs may also enhance or inhibit this same enzyme system, although to individually different extents, and can

* Some sources of comprehensive drug interaction information available through the Internet:

American Foundation for AIDS Research (AMFAR)

Treatment Directory: <http://www.amfar.org>

Medscape HIV/AIDS Resources: <http://www.medscape.com>



lead to altered blood levels of the Rifamycin antibiotics. The potential drug to drug interactions may result in ineffectiveness of the antiretroviral drugs, to ineffective treatment of tuberculosis or to an increased risk of drug toxicity.

It is worth noting that:

- Rifabutin, can be used with all PIs (except Saquinavir) and with all NNRTIs (except Delavirdine), although dosage adjustments are sometimes necessary.
- Isoniazid, which is recommended for the preventive therapy of tuberculosis, is free from any interactive effect with PIs and NNRTIs.
- The Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are not metabolised by the cytochrome P450 enzyme system and are free from interaction with either of the Rifamycin antibiotics.

Tuberculosis is an important public health problem in many resource-limited countries and also a common “opportunistic infection” in HIV infected individuals.

With time, as the use of antiretroviral drugs increases, it is likely that the concurrent treatment of these two infections will become more frequent.

It has been suggested that in resource limited settings, patients with active tuberculosis should not commence ART until chemotherapy for tuberculosis has been completed. While this would greatly simplify treatment regimens and enhance adherence, the effects of this approach on the overall outcomes of treatment have not been fully evaluated and further research is needed.

In general, the treatment of tuberculosis should be in accordance with the recommendations of the National Tuberculosis Programme in each country.¹

Since Rifabutin is often not available in resource limited countries, the following are possible options for the treatment of tuberculosis in patients receiving ART, which are drawn from published guidelines.^{2,3}

Possible options for ART in patients with active Tuberculosis (TB)

- Defer ART until TB treatment is completed
- Defer ART until ‘the continuation phase’ of treatment for TB and use Ethambutol + Isoniazid as continuation.
- Treat TB with Rifampin containing regimen and use Ritonavir + 2 NRTIs*
- Treat TB with Rifampin containing regimen and use Ritonavir/Saquinavir + 2 NRTIs*
- Treat TB with Rifampin containing regimen and use Efavirenz + 2 NRTIs*
- Treat TB with Rifampin containing regimen and use a 2 NRTIs regimen, then change to maximally suppressive ART once TB treatment is completed.

3.6.2. INTERACTIONS WITH DRUGS COMMONLY USED FOR THE PREVENTION AND TREATMENT OF OIs

Trimethoprim/Sulfamethoxazole, Ganciclovir and Hydroxyurea can potentially cause additive haematologic toxicity when given together with

* Clinical experience and pharmacokinetic data on these combinations are still limited.

¹ **Treatment of Tuberculosis: Guidelines for National Programmes.** World Health Organisation. 2nd Edition 1997.

² **Safe and effective use of antiretrovirals.** Module 4, Guidance Modules on Antiretroviral Treatments. World Health Organisation. WHO/ASD/98.1

³ **Updated Guidelines for the Use of Rifabutin or Rifampin for the Treatment and Prevention of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors.** MMWR March 10, 2000/49 (9); 185-9



Zidovudine. In these situations, careful monitoring of haematologic indices is necessary.

Dapsone, may lead to additive neurotoxicity when used together with Stavudine, Zalcitabine, and Didanosine.

The antifungal agents Ketoconazole and Fluconazole may inhibit the metabolism of Protease Inhibitors and the resultant increase in the serum levels of PIs, increases the risk of toxicity.

3.7. FURTHER RESEARCH NEEDS

Research is vital to inform future treatment and care decisions as well as for the advancement of scientific knowledge. To date there has been a paucity of controlled clinical trials in low and middle-income countries. However some programmes such as HIV-NAT in Thailand and HIV-NET in South Africa have paved the way for successful needs based research applicable to local requirements. This has been achieved through interaction between local researchers, governments and international funding and research agencies. Such partnerships for clinical research not only provide locally applicable evidence for treatment strategies but also build research capacity in low and middle-income countries.

It is vital to ask appropriate research questions that will have an impact locally but which could also be applicable to other settings. Most treatment advances will have initially been evaluated during the licensing process in industrialised countries. Whilst not aiming at duplicating research, an evidence base for local application of ART interventions must be developed for resource limited settings.

A vast amount of medical research is underway worldwide in the field of HIV. Researchers have a

duty to establish that their studies are not unnecessarily repetitive, ask appropriate questions and do not unduly raise expectations in advance of favourable findings. The establishment of local research committees and a Data and Safety Monitoring Board for individual studies can help to maintain transparency and probity of the research process.

All research conducted must adhere to the ethical guidelines which exist in individual countries and which reflect those established by International regulatory authorities.

Suitable topics for research could be:

- Research in supportive medication and processes related to medication
- Alternative therapies including traditional approaches to care and treatment
- Assessment of cost-effectiveness of novel treatment strategies using antiretrovirals, particularly those investigating simplified regimens, new induction-maintenance regimens and pulsed/cycled antiretroviral therapy.
- Treatment and monitoring strategies adapted to resource limited settings.
- Research related to treatments which have not been studied in the populations in which they will be used
- Research on utility of treatments against local viral strains and HIV-2

3.8. INFORMATION AND TRAINING NEEDS

Quality information is the basis of good decision making in health care provision, and in-service training or continuing medical education for health personnel ensures that standards of good clinical practice are maintained. Even when antiretroviral drugs are not yet directly available or



affordable by the health systems or patients, the attention generated by these drugs in the media is such that carers need to be equipped with regularly updated information that is technically sound and regularly updated.

Information needs to be at a level appropriate for the user and in suitable language.

The targeted populations should include:

Decision-makers, Health-care professionals in both public and private sectors, Patients, Family and carers and the General Public.

Every HIV care centre accredited or regulated to provide and monitor ART should therefore design an information and training plan as an integral part of the treatment programme. This represents a cost-effective intervention in its own right and training programmes on comprehensive clinical care of HIV, including ART, should be initiated at country level and tailored to local needs.

SOME SOURCES OF INFORMATION FOR TRAINING:

The World Health Organisation

Initiative on HIV/AIDS and STI
20 Avenue Appia
CH-1211 Geneva 27
Switzerland.
Fax: 41 22 791 4834
Web site: <http://www.who.int/asd>

UNAIDS Documentation Centre

20 Avenue Appia
CH-1211 Geneva 27
Switzerland.
Web site: <http://www.unaids.org>

Enhancing Care Initiative

Harvard AIDS Institute
651 Huntington Avenue
Boston, MA 02115
USA
Web site: <http://www.eci.harvard.edu>

SHARE Educational Programme

International AIDS Society (IAS)
Rome Branch
Via dei Sabelli 195
00185 Rome
Italy
Fax: 39 06 4461400
E-mail: ias.share@flashnet.it
Web site: <http://www.ias-share.org>



TECHNICAL CONSULTATIVE MEETING TO REVIEW AND UPDATE GUIDANCE ON SAFE AND EFFECTIVE USE OF ANTIRETROVIRAL TREATMENTS

WHO HEADQUARTERS, GENEVA
15-17 FEBRUARY 2000

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Generic name Other name (Trade name®)	Recommended dosage	Special instructions Precautions	Adverse effects minor, frequent	Adverse effects serious, dose limiting
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS				
Zidovudine ZDV; AZT (Retrovir®)	300 mg (1 tablet) bid	caution in: ■ liver or renal insufficiency ■ pre-existing anaemia	initial nausea headache fatigue muscle pains	anaemia neutropenia lactic acidosis
Didanosine* ddl (Videx®)	200 mg (2 tablets) bid weight below 60 kg: 100mg bid	■ to increase oral bioavailability take 1 hour before or after food ■ contains antacid, affects absorption of other drugs	neuropathy nausea diarrhea	pancreatitis lactic acidosis
Zalcitabine* ddC (Hivid®)	0.75 mg (1 tablet) tid weight below 40 kg: 0.375 mg tid		neuropathy oral ulcers	pancreatitis lactic acidosis
Stavudine* d4T (Zerit®)	40 mg (1 capsule) bid weight below 60 kg.: 30 mg bid	caution in liver insufficiency	neuropathy	lactic acidosis
Lamivudine (3TC) (EpiVir®)	150 mg (1 tablet) bid		generally well tolerated	lactic acidosis
Lamivudine + Zidovudine (Combivir®)	1 tablet bid	caution in: ■ liver or renal insufficiency ■ pre-existing anaemia	initial nausea headache fatigue muscle pains	anaemia neutropenia lactic acidosis
Abacavir (Ziagen®)	300 mg (1 tablet) bid	caution in: ■ liver or renal insufficiency discontinue use if symptoms of hypersensitivity occur	nausea poor appetite vomiting fatigue sleep disturbance	hypersensitivity reaction lactic acidosis
NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS				
Nevirapine (Viramune®)	200 mg (1 tablet) once a day, for 14 days; followed by 200 mg bid	caution in liver disease	skin rash abnormal liver function tests	hepatitis
Delavirdine (Rescriptor®)	400 mg (4 tablets) tid	caution in liver disease	skin rash headaches abnormal liver function tests	hepatitis
Efavirenz (Sustiva®)	600 mg (3 capsules), once a day	caution in liver disease	skin rash neuropsychiatric disturbances abnormal liver function tests	hepatitis
PROTEASE INHIBITORS				
Saquinavir** hard gel capsule (Invirase®)	600 mg (3 capsules) tid	■ take with high fat meal to aid absorption ■ caution in liver disease	diarrhoea nausea abnormal liver function tests	hypreglycaemia lipodystrophy abnormal bleeding
Saquinavir* hard gel capsule (Fortovase®)	1600 mg (8 capsules) bid or 1200 mg (6 capsules) tid	■ take with high fat meal ■ refrigeration for long term storage ■ caution in liver disease	diarrhoea nausea abnormal liver function tests	hypreglycaemia lipodystrophy abnormal bleeding
Ritonavir (Norvir®)	600 mg (6 capsules) bid (begin with 300 mg bid and escalate over 10 days)	■ capsules require refrigeration ■ easier tolerated if taken with food	nausea diarrhoea weakness skin sensitivity perioral tingling and numbness change in taste	hyperglycaemia lipodystrophy abnormal bleeding
Indinavir (Crixivan®)	800 mg (2 capsules) tid	■ take on an empty stomach ■ drink 1.5 litres of liquid per day to avoid kidney problems ■ report any loin pain or blood in urine	nausea pain in belly headache	kidney stones hyperglycaemia lipodystrophy abnormal bleeding
Nelfinavir (Viracept®)	750 mg (3 tablets) tid or 1250 mg (5 tablets) bid	■ to be taken with food	diarrhoea nausea flatulence skin rash	hyperglycaemia lipodystrophy abnormal bleeding
Amprenavir (Agenerase®)	1200 mg (8 capsules) bid	■ decreased absorption if taken with fatty meal	nausea vomiting diarrhoea perioral numbness altered taste mood disorders	hypersensitivity rash

* Dosage adjustments necessary for patients with reduced body weight (bwt)

** Saquinavir is available in two formulations, a hard-gel capsule (Invirase) and a soft-gel capsule (Fortovase). Saquinavir as the hard-gel capsule is poorly absorbed and is generally recommended for use in combination with ritonavir that enhances its bioavailability through a drug-drug interaction. Saquinavir as the soft-gel capsule is better absorbed and may be used with or without ritonavir.

For orders, contact :

World Health Organization, Distribution and Sales
20 Avenue Appia , CH-1211 Geneva 27, Switzerland
Phone: +41 22 791 2476
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UNAIDS Information centre
20 Avenue Appia, CH-1211 Geneva 27, Switzerland
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