



**SCALING UP ANTIRETROVIRAL
THERAPY IN RESOURCE-LIMITED
SETTINGS:
TREATMENT GUIDELINES FOR
A PUBLIC HEALTH APPROACH**

2003 REVISION



WORLD HEALTH ORGANIZATION
DEPARTMENT OF HIV/AIDS

The creation of the present guidelines would not have been possible without the participation of numerous experts.

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Abbreviations

ABC	abacavir	MTCT	mother-to-child transmission (of HIV)
ACTG	AIDS Clinical Trials Group	NAM	nucleoside analogue mutation
AIDS	acquired immunodeficiency syndrome	NFV	nelfinavir
ALT	alanine aminotransferase	NGO	nongovernmental organization
ART	antiretroviral therapy	NNRTI	non-nucleoside reverse transcriptase inhibitor
ARV	antiretroviral	NsRTI	nucleoside analogue reverse transcriptase inhibitor
ATV	atazanavir	NtRTI	nucleotide analogue reverse transcriptase inhibitor
bid	twice daily	NVP	nevirapine
CD4	T-lymphocyte CD4+	PCR	polymerase chain reaction
CNS	central nervous system	PI	protease inhibitor
d4T	stavudine	qd	once daily
DART	development of antiretroviral therapy in Africa	RT	reverse transcriptase
ddl	didanosine	RTI	reverse transcriptase inhibitor
DOT	directly observed therapy	RTV	ritonavir
EFV	efavirenz	RTV-PI	ritonavir-boosted protease inhibitor
ENF (T-20)	enfuvirtide	sgc	soft gel capsule
FBC	full blood count	SQV	saquinavir
FDC	fixed-dose combination	TB	tuberculosis
FTC	emtricitabine	TDF	tenofovir disoproxil fumarate
GI	gastrointestinal	TLC	total lymphocyte count
HAART	highly active antiretroviral therapy	UN	United Nations
Hgb	haemoglobin	UNAIDS	Joint United Nations Programme on HIV/AIDS
HIV	human immunodeficiency virus	WBC	white blood cell
HIVab	human immunodeficiency virus antibody	WHO	World Health Organization
IDU	injecting drug user	ZDV	zidovudine (also known as AZT)
IDV	indinavir	/r	low dose ritonavir
LPV	lopinavir		

1. INTRODUCTION

The advent of potent antiretroviral therapy (ART) in 1996 led to a revolution in the care of patients with HIV/AIDS in the developed world. Although the treatments are not a cure and present new challenges with respect to side-effects and drug resistance, they have dramatically reduced rates of mortality and morbidity, have improved the quality of life of people with HIV/AIDS, and have revitalized communities. Moreover, HIV/AIDS is now perceived as a manageable chronic illness rather than as a plague ¹. Unfortunately, most of the 40 million people currently living with HIV/AIDS reside in developing countries and do not share this vastly improved prognosis ². WHO conservatively estimated that, at the end of 2003, some 6 million people in developing countries were in immediate need of life-sustaining ART. However, only about 400 000 persons were being treated, over a third of them in Brazil. At the UN General Assembly High-Level Meeting on HIV/AIDS on 22 September 2003, WHO declared that the lack of access to HIV treatment was a global health emergency. WHO calls for unprecedented action to ensure that by the end of 2005 at least 3 million people in need of ART will have access to it.

In order to achieve this target, WHO will develop a strategic framework with the following pillars:

- ▶ global leadership, strong partnership and advocacy;
- ▶ urgent sustained country support;
- ▶ simplified standardized tools for the delivery of ART;
- ▶ an effective and reliable supply of medicines and diagnostics;
- ▶ rapid identification and reapplication of new knowledge and success.

The present updated and simplified treatment guidelines are a cornerstone of the WHO 3-by-5 Plan and are more directive than its predecessor with respect to first-line and second-line therapies. They take into account not only the evidence generated by clinical trials and observational studies on the efficacy and side-effects of the treatment regimens discussed, but also the experience gained with ART by programmes in resource-limited settings and the cost and availability of drugs in those settings. By taking this approach, WHO seeks to assist countries and regions in providing effective antiretroviral therapy to the millions of individuals in immediate or imminent

need of treatment. This document, dealing with recommendations for ARV treatment and monitoring, is intended to be a component of a comprehensive package of care at the country level, including the prevention and treatment of opportunistic infections, nutritional programmes and psychosocial support for infected persons. Treatment for HIV, facilitated by these guidelines, complements the full range of HIV prevention efforts for uninfected people at the country level.

The following recent advances in the ART field have been considered in the preparation of this revision:

- ▶ clinical trial data, including those suggesting the inferior virological efficacy of the triple nucleoside combination, ZDV/3TC/abacavir (ABC) in comparison with a three-drug or four-drug efavirenz-based regimen;
- ▶ the availability of the nucleotide analogue, tenofovir disoproxil fumarate (TDF);
- ▶ toxicity concerns regarding the dual nucleoside component of stavudine (d4T)/didanosine (ddl);
- ▶ increasing recognition of the extent of drug class cross-resistance among the nucleoside and nucleotide analogues;
- ▶ the approval of a new nucleoside analogue, emtricitabine (FTC), a protease inhibitor, atazanavir (ATV), the fusion inhibitor, enfuvirtide (ENF, T-20) and increasing availability and clinical experience with generic ARV preparations, particularly in fixed-dose combinations and blister packs (ENF will not be considered further in this document because of the requirement for parenteral administration and the cost of the drug, making it impractical for use in resource-limited settings).

These treatment guidelines are part of WHO's commitment to the treatment of persons living with HIV/AIDS. The first edition of these recommendations, published in April 2002, reflected the best practices at that time on the basis of a review of evidence. In this rapidly evolving field, WHO recognized at the outset that the recommendations would have to be regularly updated. The present revision has been brought forward as a result of new scientific data and the increasing reality of ART scale-up in many countries.

II. DOCUMENT OBJECTIVES

Currently, fewer than 5% of people in developing countries who need ART can access the medicines in question. WHO believes that at least 3 million people needing care should be able to get the medicines by 2005. This represents almost a tenfold increase.

These treatment guidelines are intended to support and facilitate the proper management and scale-up of ART in the years to come by proposing a public health approach to achieve the goals. The key tenets of this approach are as follows.

- 1) Scaling-up of antiretroviral treatment programmes with a view to universal access, i.e. all persons requiring treatment as indicated by medical criteria should have access to it.
- 2) Standardization and simplification of ARV regimens so as to support the efficient implementation of treatment programmes in resource-limited settings.
- 3) Ensuring that ARV treatment programmes are based on scientific evidence in order to avoid the use of substandard protocols that compromise the outcomes of individual patients and create a potential for the emergence of drug-resistant virus. However, it is also important to consider the realities with respect to the availability of human resources, health system infrastructures and socioeconomic contexts so that clear and realistic recommendations can be made.

While it is hoped that this document will be useful to clinicians in resource-limited settings, it is primarily intended for use by treatment advisory boards, national AIDS programme managers and other senior policy-makers who are involved in the planning of national and international HIV care strategies in developing countries. The treatment guidelines serve as a framework for selecting the most potent and feasible ARV regimens as components of expanded national responses for the care of HIV-infected individuals. The framework aims to standardize and simplify antiretroviral therapy, as with tuberculosis (TB) treatment in national TB control programmes, while acknowledging the relative complexity of HIV treatment. Accordingly, options for first-line and second-line regimens are presented, bearing in mind the need to strengthen health systems that often lack staffing power and monitoring facilities, with a view to maximizing the quality and outcomes of the treatments offered.

The guidelines consider when ART should begin, which ARV regimens should be introduced, the reasons for changing ART and the regimens that should be continued if treatment has to be changed. They also address how treatment should be monitored, with specific reference to the side-effects of ART and drug adherence, and make specific recommendations for certain subgroups of patients.

III. WHEN TO START ARV THERAPY IN ADULTS AND ADOLESCENTS

WHO recommends that, in resource-limited settings, HIV-infected adults and adolescents should start ARV therapy when the infection has been confirmed and one of the following conditions is present.

- ▶ Clinically advanced HIV disease:
 - ▶ WHO Stage IV HIV disease, irrespective of the CD4 cell count;
 - ▶ WHO Stage III disease with consideration of using CD4 cell counts $<350/\text{mm}^3$ to assist decision-making.
- ▶ WHO Stage I or II HIV disease with CD4 cell counts $<200/\text{mm}^3$ (Table A).

The rationale for these recommendations is as follows. The treatment of patients with WHO Stage IV disease (clinical AIDS) should not be dependent on a CD4 cell count determination. However, where available, this test can be helpful in categorizing patients with Stage III conditions with respect to their need for immediate therapy. For example, pulmonary TB can occur at any CD4 count level and, if the CD4 cell count level is well maintained (i.e. $>350/\text{mm}^3$), it is reasonable to defer therapy and continue to monitor the patient. For Stage III conditions a threshold of $350/\text{mm}^3$ has been chosen as the level below which immune deficiency is clearly present such that patients are eligible for treatment when their clinical condition portends rapid clinical progression. A level of $350/\text{mm}^3$ is also in line with other consensus guideline documents^{3, 4}. For patients with Stage I or Stage II HIV disease the presence of a CD4 cell count $<200/\text{mm}^3$ is an indication for treatment.

In cases where CD4 cell counts cannot be assessed the presence of a total lymphocyte count of $1200/\text{mm}^3$ or below may be used as a substitute indication for treatment in the presence of symptomatic HIV disease (i.e. WHO Stages II or III). While the total lymphocyte count correlates relatively poorly with the CD4 cell count in asymptomatic persons, in combination with clinical staging it is a useful marker of prognosis and survival⁵⁻¹⁰. An assessment of viral load (e.g. using plasma HIV-1 RNA levels) is not considered necessary before starting therapy. Because of the cost and complexity of viral load testing, WHO does not

currently recommend its routine use in order to assist with decisions on when to start therapy in severely resource-constrained settings. It is hoped, however, that increasingly affordable methods of determining viral load will become available so that this adjunct to treatment monitoring can be more widely employed.

It should be noted that the current WHO Staging System for HIV Infection and Disease for Adults and Adolescents was developed several years ago and has consequent limitations. Adaptations at the level of national programmes may therefore be appropriate. Nevertheless, it remains a useful tool for assisting in defining parameters for initiating therapy in resource-limited settings and thus has continued to be applied in this revision.

TABLE A. RECOMMENDATIONS FOR INITIATING ANTIRETROVIRAL THERAPY IN ADULTS AND ADOLESCENTS WITH DOCUMENTED HIV INFECTION

<p>If CD4 testing available:</p> <ul style="list-style-type: none"> ▶ WHO Stage IV disease, irrespective of CD4 cell count ▶ WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), with consideration of using CD4 cell counts <350/mm³ to assist decision-making^a ▶ WHO Stage I or II disease with CD4 cell counts 200/mm³^b
<p>If CD4 testing unavailable:</p> <ul style="list-style-type: none"> ▶ WHO Stage IV disease, irrespective of total lymphocyte count ▶ WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), irrespective of the total lymphocyte count ▶ WHO Stage II disease with a total lymphocyte count 1200/mm³^c

^a CD4 count advisable to assist with determining need for immediate therapy. For example, pulmonary TB may occur at any CD4 level and other conditions may be mimicked by non-HIV etiologies (e.g. chronic diarrhoea, prolonged fever).

^b The precise CD4 level above 200/mm³ at which ARV treatment should start has not been established.

^c A total lymphocyte count of 1200/mm³ can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms (Stage II or III) exist. It is not useful in the asymptomatic patient. Thus, in the absence of CD4 cell testing, asymptomatic HIV-infected patients (WHO Stage I) should not be treated because there is currently no other reliable marker available in severely resource-constrained settings.

IV. RECOMMENDED FIRST-LINE ARV REGIMENS IN ADULTS AND ADOLESCENTS

Countries are encouraged to use a public health approach to facilitate the scale-up of ARV use in resource-limited settings as delineated in the WHO 3-by-5 Plan. This means that ART programmes should be developed which can reach as many people as possible who are in need of therapy and requires that ARV treatment be standardized. In particular, it is suggested that countries select a first-line regimen and a limited number of second-line regimens, recognizing that individuals who cannot tolerate or fail the first-line and second-line regimens will be referred for individualized care by specialist physicians. The use of standardized regimens is an essential component of the 3-by-5 Plan and will facilitate WHO's efforts to assist Member States with achieving this goal. This is the approach to ARV regimen selection taken in the present document.

Among the factors that should be considered in the selection of ART regimens at both the programme level and the level of the individual patient are:

- ▶ potency;
- ▶ side-effect profile;
- ▶ laboratory monitoring requirements;
- ▶ potential for maintenance of future treatment options;
- ▶ anticipated patient adherence;
- ▶ coexistent conditions (e.g. coinfections, metabolic abnormalities);
- ▶ pregnancy or the risk thereof;
- ▶ use of concomitant medications (i.e. potential drug interactions);
- ▶ potential for infection with a virus strain with diminished susceptibility to one or more ARVs, including that resulting from prior exposure to ARVs given for prophylaxis or treatment;
- ▶ very importantly, availability and cost.

The use of quality-assured^a antiretrovirals in fixed-dose combinations (FDCs)^b or as blister packs^c is another important consideration as this promotes better adherence and, in turn, limits the emergence of drug resistance. It also facilitates ARV storage and distribution logistics. Additional considerations relevant to the developing world include access to a limited number of ARV drugs, limited health service infrastructures (including human resources), the need to deliver drugs to rural areas, high incidences of TB and hepatitis B and/or C in populations and the presence of varied HIV types, groups and subtypes.

The previous (April 2002) version of these treatment guidelines recommended that countries should select a first-line treatment regimen and identified regimens composed of two nucleosides plus either a non-nucleoside, or abacavir, or a protease inhibitor as possible choices. Since that version was published, many countries have started ARV treatment programmes and have chosen their first-line treatment regimens, taking into account how the above factors would come into play in the different settings. The majority of treatment programmes in developing countries have opted for a regimen composed of two nucleosides and a non-nucleoside RT inhibitor. Triple nucleoside regimens including abacavir were almost never selected because of their cost and concerns over hypersensitivity reactions, and regimens containing a protease inhibitor became secondary options, mainly because of their cost, notwithstanding price decreases. However, high pill counts, their side-effect profile and more difficult logistics (some requiring a cold chain) were probably also considerations.

The Writing Committee examined non-nucleoside-based regimens and took account of clinical experience with the efficacy and toxicity of the nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) components, the availability of fixed-dose combinations (Annex D), the lack of a requirement for a cold chain, and drug availability and cost. On this basis the Committee concluded that the four first-line ARV regimens listed in Table B were appropriate for adults and adolescents. These regimens

^a Quality-assured medicines assembled in fixed-dose combinations (FDCs), in the context of this document, include individual products which have been deemed to meet or exceed international standards for quality, safety and efficacy. In the case of drug combinations whose components are from different manufacturers the international standards include a requirement for clinical bioequivalence studies to establish therapeutic interchangeability of the components. For WHO's work on prequalification

of ARVs see: <http://www.who.int/medicines/organization/qsm/activities/pilotproc/proc.shtml>

^b Fixed-dose combinations are based on the principle of inclusion of two or more active pharmacological products in the same pill, capsule, tablet or solution.

^c A blister pack is a plastic or aluminum blister containing two or more pills, capsules or tablets.

consist of a thymidine analogue NRTI, i.e. stavudine (d4T) or zidovudine (ZDV), a thiacytidine NRTI, i.e. lamivudine (3TC), and an NNRTI, i.e. nevirapine (NVP) or efavirenz (EFV).

The choice between d4T and ZDV should be made at the country level on the basis of local considerations but it is recommended that both drugs be available. d4T is initially better tolerated than ZDV and does not require haemoglobin monitoring. However, among the NRTIs, it has been consistently most associated in developed countries with lipoatrophy and other metabolic abnormalities, including lactic acidosis, particularly when combined with didanosine (ddI). It can also cause peripheral neuropathy and pancreatitis. ZDV has also been implicated in metabolic complications of therapy but to a lesser extent than d4T. Initial drug-related side-effects (headache, nausea) are more frequent with ZDV and the drug can cause severe anaemia and neutropenia, which, at the very least, requires that haemoglobin should be monitored before and during treatment with ZDV. d4T can be substituted for ZDV in the event of intolerance to the latter and vice versa (except in cases of suspected lactic acidosis, in which instance neither drug should be prescribed). However, the initial need for less laboratory monitoring might, at present, favour d4T as the nucleoside of choice for the majority of patients in ART programmes in settings with severe resource limitations where rapid scaling-up is intended.

3TC is a potent NRTI with an excellent record of efficacy, safety and tolerability. It can be given once or twice daily and has been incorporated into a number of fixed-dose combinations. Emtricitabine (FTC) is a recently approved nucleoside analogue that is structurally related to 3TC, shares its resistance profile and can be given once daily¹¹. It is currently being tested as a coformulated product with tenofovir disoproxil fumarate (TDF). Because of the relatively recent approval of FTC in a limited number of countries it is not included in WHO's recommended first-line regimens but this may change in the light of future experience with the drug and its availability and cost.

The dual nucleoside component of d4T/ddI is no longer recommended as part of first-line regimens because of its toxicity profile, particularly in pregnant women¹². It is also worth emphasizing that ZDV and d4T should never be used together because of proven antagonism between them¹³.

TDF has a long intracellular half-life and can therefore be used as part of once-daily triple-drug regimens. It has been shown that TDF is an effective component of first-line regimens in combination with 3TC and efavirenz (EFV)^{14, 15}. It is generally well tolerated although there have been reports of renal insufficiency in patients receiving TDF¹⁶⁻¹⁸. However, worldwide experience with the drug is

still relatively limited. In addition, its limited availability and relatively high cost in developing countries continue to be significant factors. For the purposes of the present treatment guidelines, therefore, discussion of its use will be restricted to second-line therapy. As experience, availability and cost issues in resource-limited settings become clarified the inclusion of TDF in WHO-recommended first-line regimens should be reconsidered.

Globally, NNRTI-based regimens are now the most widely prescribed combinations for initial therapy. They are potent and relatively simple but are inactive in respect of HIV-2 and group O of HIV-1. EFV and NVP are both potent NNRTIs with demonstrated clinical efficacy when administered in appropriate combination regimens. However, differences in toxicity profile, a potential for interaction with other treatments, and cost, allow the formulation of both positive and negative recommendations on their use^{14, 19–25}. NVP has a higher incidence of rash, which may be severe and life-threatening, and a greater risk of hepatotoxicity, which may also be life-threatening. This makes the drug less suitable for treating patients who use other hepatotoxic medications, or drugs that can cause rash, or both, such as rifampicin. The major toxicities associated with EFV are related to the central nervous system (CNS), teratogenicity and rash. (Rash is more frequent in children than adults, is generally mild, and usually does not require discontinuation of therapy.) The CNS symptoms typically abate after 10 to 14 days in most, but not all, patients. EFV should be avoided in persons with a history of severe psychiatric illness, when there is a potential for pregnancy, and during pregnancy. EFV may be considered to be the NNRTI of choice in patients with TB coinfection, and NVP may be the best choice in women of childbearing potential or who are pregnant. EFV should not be given to women of childbearing potential unless effective contraception can be assured. However, it is important to emphasize that EFV and NVP may interact with estrogen-based contraceptive pills. NVP is available as part of three-drug FDC which could be used when assured-quality formulations of proven bioequivalence are available.

The use of the five-drug formulary approach (d4T or ZDV) + 3TC + (NVP or EFV) translates practically into four possible regimens (Table B) and provides options for drug substitutions in respect of toxicity (Table C). Because each is considered an appropriately potent, standard-of-care regimen with respect to efficacy, other factors should determine what a country chooses as a lead regimen. Table B lists some of the factors that should be taken into account in making this decision. ARVs in FDCs and blister packs have potential advantages over conventional drug packaging: they are helpful tools for simplifying treatment and promote adherence. Moreover, they can minimize prescription errors, improve adherence of health care workers to treatment standards, decrease

errors in drug administration, improve drug management (because of fewer items and a single expiration date), simplify drug forecasting, procurement, distribution and stocking because fewer items and lower volumes are necessary, and reduce the risk of misuse of single drugs. FDCs also present challenges with respect to the individualization of dosing of individual components, the treatment of children and the differential half-lives of drugs when treatment is interrupted. Laboratory monitoring requirements should also be taken into account (see Section VI).

When d4T/3TC/NVP or ZDV/3TC/NVP is chosen as the first-line regimen the availability of the two-drug combination (d4T/3TC or ZDV/3TC) is also important for use with NVP lead-in dosing during the first two weeks of treatment and for managing some toxicities associated with NVP (Annex D). Additional drugs should be available in districts (level 2) or regional hospitals (level 3). This tiered approach to ARV regimen availability can be paralleled by a tiered monitoring strategy for health care systems (see Section VI).

TABLE B. FIRST-LINE ARV REGIMENS IN ADULTS AND ADOLESCENTS AND CHARACTERISTICS THAT CAN INFLUENCE CHOICE

ARV regimen	Major potential toxicities	Usage in women (of childbearing age or pregnant)
d4T/3TC/NVP	d4T-related neuropathy, pancreatitis and lipoatrophy; NVP-related hepatotoxicity and severe rash	Yes
ZDV/3TC/NVP	ZDV-related GI intolerance, anaemia, and neutropenia; NVP-related hepatotoxicity and severe rash	Yes
d4T/3TC/EFV	d4T-related neuropathy, pancreatitis and lipoatrophy; EFV-related CNS toxicity and potential for teratogenicity	No ^b
ZDV/3TC/EFV	ZDV-related GI intolerance, anaemia and neutropenia; EFV-related CNS toxicity and potential for teratogenicity	No ^b

^a See Section VIII.C (People with TB disease and HIV coinfection).

^b See Section VIII.A (Women of childbearing potential or who are pregnant).

^c These combinations have not been prequalified by WHO but could be used if assured-quality formulations of proven bioequivalence were available.

^d Obtained from: *Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS*, June 2003 (www.who.int/HIV_AIDS).

Usage in TB coinfection ^a	Availability as three-drug fixed-dose combination	Laboratory monitoring requirements	Price for least-developed countries, June 2003 (US\$/year) ^d
Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens ^a	Yes	No	281–358
Yes in rifampicin-free continuation phase of TB treatment. Use with caution in rifampicin-based regimens ^a	Yes ^c	Yes	383–418
Yes, but EFV should not be given to pregnant women or women of childbearing potential, unless effective contraception can be assured	No. EFV not available as part of FDC; however partial FDC available for d4T/3TC ^c	No	350–1086
Yes, but EFV should not be given to pregnant women or women of childbearing potential unless effective contraception can be assured	No. EFV not available as part of FDC; however, partial FDC available for ZDV/3TC	Yes	611–986

ADDITIONAL CONSIDERATIONS FOR FIRST-LINE THERAPY INCLUDING TREATMENT OF HIV-2 AND GROUP O HIV-1 INFECTIONS

PI-based regimens. While PI-based regimens remain an accepted standard of care for initial regimens, their high cost relative to NNRTI-based regimens makes their use problematic in resource-limited countries seeking to achieve rapid scale-up of therapy. Advantages of PI-based regimens (e.g. PI plus two NRTIs), however, are proven clinical efficacy and well-described toxicities. Disadvantages are higher pill counts, food and water requirements in some cases, significant interactions with other drugs that preclude or complicate their use during TB treatment regimens using rifampicin, metabolic abnormalities and the need for a functioning cold chain for ritonavir-boosted regimens. Consequently, in these treatment guidelines, PI-based regimens are primarily reserved for second-line therapy (Section VII). They should be considered as first-line regimens, however, in circumstances where there is concern for the presence of NNRTI resistance (e.g. prevalence in the community exceeding 5–10%)²⁶, where there are viral types with known insensitivity to NNRTIs (e.g. HIV-2 or HIV-1 group O) or where there is intolerance of the NNRTI class of agents. Considerations include (d4T or ZDV) + 3TC combined with either lopinavir/ritonavir (LPV/r), saquinavir/ritonavir (SQV/r), indinavir/ritonavir (IDV/r), or nelfinavir (NFV), the choice(s) being dictated by national programme priorities. Ritonavir-boosted PIs are becoming preferred because of their high potency²⁷ and relatively lower pill burden, but the requirement for a cold chain and the support of frequent laboratory monitoring present problems for many low-resource countries. LPV/r is administered as a twice-daily regimen and is relatively well tolerated, but frequently causes elevations in plasma lipid levels. SQV/r can be administered once daily is known to achieve adequate blood levels in pregnancy and is compatible with rifampicin coadministration. However the pill burden with currently available formulations is high and gastrointestinal side-effects are frequent. NFV, although considered less potent than LPV/r, is an acceptable alternative, has been used extensively in pregnancy and does not require cold chain facilities. However, it is less effective against HIV-2 infection than other PIs^{28–30}. IDV/r also can be considered an alternative but is associated with a moderate incidence of renal adverse effects, particularly nephrolithiasis, and requires vigorous hydration.

The role of the recently approved protease inhibitor, atazanavir (ATV) in resource-limited settings is currently unclear. The drug has the advantage of once-daily administration and does not induce hyperlipidaemia when administered without ritonavir boosting. It can also be given with low-dose ritonavir to enhance its

potency^{31–33}. It is a reasonable alternative but much greater experience has been gained with the other PIs listed. Firmer recommendations will be made as the cost and availability of ATV, and experience with the drug, become clearer.

Triple NRTI-based regimens. In the 2002 edition of these guidelines the ZDV/3TC/abacavir (ABC) regimen was considered the most user-friendly with respect to both patients and programmes (two pills per day and absence of significant drug interactions). The main disadvantages noted were uncertainty about its potency when the viral load was very high in patients with advanced disease, uncertainty as to whether the drugs, particularly ABC, would become available at an affordable cost, and the potential for fatal ABC hypersensitivity reactions. Recently released data from ACTG A5095 Study demonstrate that ZDV/3TC/ABC had a significantly higher virological failure rate than the other two study arms combined (ZDV/3TC/EFV or ZDV/3TC/ABC/EFV), 21% vs. 10% respectively, with a median follow-up of 32 weeks³⁴. Importantly, significant differences in virological outcome were seen in persons with viral loads above and below 100 000 HIV RNA copies/ml. The study remains blinded with respect to the two EFV-containing arms. The incorporation of these findings into clinical practice and guidelines policy presents challenges because of the perceived advantages of triple nucleoside regimens, especially their attractiveness in the setting of coinfection with TB. It is important to note that the efficacy of ZDV/3TC/ABC in ACTG A5095 was comparable to that reported in previously reported studies of this regimen in the treatment of naive persons^{35, 36}. Moreover, in ACTG A5095 the CD4 cell responses were comparable to those of the combined EFV-containing arms. Thus, its virological inferiority to EFV-based regimens in a directly comparative trial moves this triple NRTI combination to a lower tier of consideration but does not, and should not, remove it from serious consideration. It may be useful, for example, when NNRTIs cannot be used because of intolerance or drug resistance and when PI-based regimens are not available. In particular, this regimen is a viable alternative for the management of patients coinfecting with TB when antiretroviral and anti-TB therapy are coadministered. For the purposes of these guidelines it is considered to be a secondary alternative for initial therapy in specific situations (e.g. active TB coinfection, HIV-2 infection). It is also important to note that the ongoing DART trial will provide crucial additional information on the safety of ZDV/3TC/ABC in comparison with ZDV/3TC/TDF and ZDV/3TC/NVP in 3000 treatment-naive patients in Africa³⁷.

It should not be assumed that any triple NRTI regimen is comparable to any other: each triple NRTI combination needs to be evaluated on its own merits. Illustrative of this is the recently presented study of the combination of TDF/3TC/ABC administered once daily, in which there was a high virological failure

rate (49%) and a high incidence of the K65R mutation, which confers cross-resistance to non-ZDV nucleoside analogues³⁸. This specific combination should be avoided in the light of these data. Similarly, in a 24-patient pilot study, TDF/ddI/3TC dosed once daily resulted in a 91% virological failure rate and a high incidence of the K65R mutation³⁹. Another recent study reported low efficacy and a high frequency of adverse events with d4T/ddI/ABC⁴⁰. These combinations should be avoided.

V. REASONS FOR CHANGING ART IN ADULTS AND ADOLESCENTS

It may be necessary to change ART because of either toxicity or treatment failure.

TOXICITY

Toxicity is related to the inability to tolerate the side-effects of medication and to the significant organ dysfunction that may result. This can be monitored clinically on the basis of patient reporting and physical examination, and there may also be a limited number of laboratory tests, depending on the specific combination regimen that is utilized and the health care setting.

If a change in regimen is needed because of treatment failure, a new second-line regimen becomes necessary. When the toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with another drug that does not have the same side-effects, e.g. substitution of d4T for ZDV (for anaemia) or NVP for EFV (for CNS toxicity or pregnancy). Given the limited number of ARV combination options available in resource-limited settings, it is preferable to pursue drug substitutions where feasible so that premature switching to completely new alternative regimens is minimized. Table C lists the first-level medication switch options for toxicity for the four combination regimens listed in Table B. For life-threatening or more complex clinical situations, referral to district or regional hospital centres is recommended.

TREATMENT FAILURE

Treatment failure can be defined clinically as assessed by disease progression, immunologically using measurement of the CD4 counts, and/or virologically by measuring viral loads. Clinical disease progression should be differentiated from the immune reconstitution syndrome, an entity that can be seen early after ARV is introduced. This syndrome is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent ARV therapy in the setting of advanced immunodeficiency, as an inflammatory response to previously subclinical opportunistic infection. It is also possible that this immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

TABLE C. MAJOR POTENTIAL TOXICITIES OF FIRST-LINE ARV REGIMENS AND RECOMMENDED DRUG SUBSTITUTIONS

Regimen	Toxicity	Drug substitution
d4T/3TC/NVP	<ul style="list-style-type: none"> • d4T-related neuropathy or pancreatitis • d4T-related lipoatrophy • NVP-related severe hepatotoxicity • NVP-related severe rash (but not life-threatening) • NVP-related life-threatening rash (Stevens-Johnson syndrome) 	<ul style="list-style-type: none"> • Switch d4T ZDV • Switch d4T TDF or ABC ^a • Switch NVP EFV (except in pregnancy) • Switch NVP EFV • Switch NVP PI ^b
ZDV/3TC/NVP	<ul style="list-style-type: none"> • ZDV-related persistent GI intolerance or severe haematological toxicity • NVP-related severe hepatotoxicity • NVP-related severe rash (but not life-threatening) • NVP-related life-threatening rash (Stevens-Johnson syndrome) 	<ul style="list-style-type: none"> • Switch ZDV d4T • Switch NVP EFV (except in pregnancy; in this situation switch to NFV, LPV/r or ABC) • Switch NVP EFV • Switch NVP PI ^b
d4T/3TC/EFV	<ul style="list-style-type: none"> • d4T-related neuropathy or pancreatitis • d4T-related lipoatrophy • EFV-related persistent CNS toxicity 	<ul style="list-style-type: none"> • Switch d4T ZDV • Switch d4T TDF or ABC ^a • Switch EFV NVP
ZDV/3TC/EFV	<ul style="list-style-type: none"> • ZDV-related persistent GI intolerance or severe haematological toxicity • EFV-related persistent CNS toxicity 	<ul style="list-style-type: none"> • Switch ZDV d4T • Switch EFV NVP

^a Switching off d4T typically does not reverse lipoatrophy but may slow its progression. TDF and ABC can be considered as alternatives but availability is currently limited in resource-constrained settings. In the absence of TDF or ABC availability, ddI or ZDV are additional alternatives to consider.

^b PI can be LPV/r or SQV/r. IDV/r or NFV can be considered as alternatives (see text).

Definitions of clinical and CD4-related treatment failure are listed in Table D. As viral loads are not normally available in resource-limited settings it is recommended that programmes primarily use clinical, and, where possible, CD4 count criteria, in order to define treatment failure. Similarly, drug resistance testing will not become a routine part of clinical care in resource-limited settings in the foreseeable future and so is not considered in these recommendations. However, it should be recognized that, in the developing world, treatment failure will be recognized later solely on the basis of clinical and/or CD4 criteria, thus providing a greater opportunity for drug resistance mutations to evolve before regimen change. This can compromise the NRTI component of the alternative regimen through drug class cross-resistance. (See Section VII.)

TABLE D. CLINICAL AND CD4+ CELL COUNT DEFINITIONS OF TREATMENT FAILURE IN HIV+ ADULTS AND ADOLESCENTS

Clinical signs of treatment failure	CD4 cell criteria for treatment failure
<ul style="list-style-type: none"> • Occurrence of new opportunistic infection or malignancy signifying clinical disease progression. This must be differentiated from the immune reconstitution syndrome which can occur in the first three months following the initiation of ART. ^a The latter does not signify treatment failure and the opportunistic infection should be treated as usual, without changes in the antiretroviral regimen. • Recurrence of previous opportunistic infection. ^b • Onset or recurrence of WHO Stage III conditions (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, recurrent invasive bacterial infections, or recurrent/persistent mucosal candidiasis). 	<ul style="list-style-type: none"> • Return of CD4 cell to pretherapy baseline or below without other concomitant infection to explain transient CD4 cell decrease. ^c • >50% fall from therapy CD4 peak level without other concomitant infection to explain transient CD4 cell decrease. ^c

^a Immune reconstitution syndrome (IRS) is characterized by the appearance of signs and symptoms of an opportunistic disease a few weeks after the start of potent antiretroviral therapy in the setting of advanced immunodeficiency, as an inflammatory response to previously subclinical opportunistic infection. It is also possible that this immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

^b Recurrence of TB may not represent HIV disease progression, as reinfection may occur. Clinical evaluation is necessary.

^c If patient is asymptomatic and treatment failure is being defined by CD4 cell criteria alone, consideration should be given to performing a confirmatory CD4 cell count if resources permit.

VI. CLINICAL AND LABORATORY MONITORING

WHO recommends that in resource-limited settings the basic clinical assessment before the initiation of ART include documentation of past medical history, identification of current and past HIV-related illnesses, identification of coexisting medical conditions that may influence the timing of initiation and choice of ART (such as TB or pregnancy), and current symptoms and physical signs. Active TB should be managed in accordance with national TB control programmes.

In order to facilitate the scale-up of ARV use in resource-limited settings, WHO has tiered its monitoring recommendations to primary health care centres (level 1), district hospitals (level 2) and regional referral centres (level 3) (Table E). WHO recognizes the importance of laboratory monitoring for efficacy and safety but does not want restricted infrastructure for these tests to place undue limitations on the scale-up effort.

TABLE E. RECOMMENDED TIERED LABORATORY CAPABILITIES FOR ARV MONITORING IN LIMITED-RESOURCE SETTINGS ^a

Primary health care centres (level 1)	District hospitals (level 2)	Regional referral centres (level 3)
Rapid HIVab testing	Rapid HIVab testing	Rapid HIVab testing
Haemoglobin (if ZDV is being considered for use) ^b	Capability to resolve indeterminate rapid HIVab test by second serological method	FBC and differential
Pregnancy testing ^d	FBC and differential	CD4+ cell count ^c
Referral for sputum smear for TB (if microscopy not available)	CD4+ cell count ^c	Full serum chemistries (including but not restricted to electrolytes, renal function, liver enzymes, lipids)
	ALT	Pregnancy testing ^d
	Pregnancy testing ^d	Sputum smear for TB
	Sputum smear for TB	Viral load testing ^e

^a This table only considers testing that is desirable for proper monitoring of ARV toxicity, efficacy and two prominent concomitant conditions (pregnancy and TB). It is not meant to be comprehensive with

respect to other diagnostic capabilities that are important in the comprehensive care of HIV-infected persons. Other resources are available for these considerations.

^b In primary health care centres where laboratory facilities are not available or in the absence of laboratory-based haemoglobinometry, the WHO haemoglobin colour scale can be used together with clinical signs to evaluate anaemia (more details at www.who.int/bct/).

^c Scale-up of ART under the 3-by-5 Plan does not require uniform CD4 testing availability but, because of the value of this test in patient monitoring, WHO will work with Member States to make this a reality.

^d EFV should not be given to women of childbearing potential unless adequate contraception is assured, not to women in the first trimester of pregnancy.

^e Because of the cost and technical issues associated with viral load testing, this test is not currently recommended as part of the present treatment guidelines. However, it is hoped that more cost-effective technologies will allow regional referral centres to acquire this capability, given its utility in assessing treatment failure.

This section concentrates on the basic clinical and laboratory monitoring indicated for the WHO-recommended first-line regimens outlined in Table B. These recommendations are designed to be implemented at the level of community health centres and/or that of district hospitals, working in concert, with backup from regional referral centres. National programme managers, working with WHO to implement the 3-by-5 Plan, should determine country-specific policies on how and where decisions about initiating therapy for individual patients are to be made. Similarly, the specific interactions of the health care delivery system levels for maximizing ART efficacy and safety require decisions to be made at the national programme level.

Clinical and laboratory assessments are considerations at baseline (pre-ART) and on treatment. Many studies conducted in developed and developing countries have demonstrated a reasonable correlation between TLC with CD4 levels in symptomatic patients ⁵⁻¹⁰. This means that even if CD4 cell count testing is unavailable, simple tools such as haemoglobin measurement and TLC can be used as laboratory markers to initiate HAART in resource-poor settings. The baseline clinical assessment is the same for all four recommended first-line regimens. It should include:

- ▶ staging of HIV disease;
- ▶ determination of concomitant medical conditions (e.g. TB, pregnancy, major psychiatric illness);
- ▶ detailing of concomitant medications, including traditional therapies;
- ▶ weight;
- ▶ assessment of patients' readiness for therapy.

Once therapy has begun, clinical assessment should cover:

- ▶ signs/symptoms of potential drug toxicities (Table D);
- ▶ adherence;
- ▶ response to therapy;
- ▶ weight;
- ▶ basic laboratory monitoring considerations as listed in Table F.

TABLE F. BASIC LABORATORY MONITORING FOR RECOMMENDED FIRST-LINE ARV REGIMENS AT PRIMARY HEALTH CARE CENTRES (LEVEL 1) AND DISTRICT HOSPITALS (LEVEL 2)

Regimen	Laboratory assessment at baseline (pretherapy)	Laboratory assessment on therapy
d4T/3TC/ NVP	Desirable but not required: CD4	Symptom-directed determination of ALT for toxicity CD4 q6–12 months, if available, for efficacy
ZDV/3TC/ NVP	Recommended: Hgb Desirable but not required: FBC, CD4	Symptom-directed determination of Hgb, WBC, ALT for toxicity CD4 q6–12 months, if available, for efficacy
d4T/3TC/ EFV	Pregnancy test (mandatory) Desirable but not required: CD4	Symptom-directed testing but none routinely required for toxicity CD4 q6–12 months, if available, for efficacy
ZDV/3TC/ EFV	Pregnancy test (mandatory) Recommended: Hgb Desirable but not required: FBC, CD4	Symptom-directed determination of Hgb, WBC for toxicity CD4 q6–12 months, if available, for efficacy

Need for scale-up of laboratory capacity

WHO recognizes the current limitations on laboratory capacity in resource-limited settings. The 3-by-5 Plan is designed to move forward with current realities in place. WHO will work with Member countries and diagnostic manufacturers to scale up laboratory infrastructure at the country level so as to permit the uniform availability of CD4 testing, wider availability of automated haematology and chemistry testing, and regional availability of viral load testing. This will require choosing uniform, cost-effective methodologies at the country level and ensuring supplies of reagents and the maintenance of equipment.

VII. CHOICE OF ARV REGIMENS IN THE EVENT OF TREATMENT FAILURE OF FIRST-LINE COMBINATIONS IN ADULTS AND ADOLESCENTS

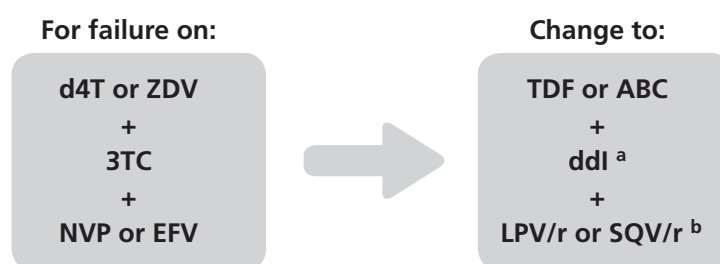
WHO recommends that the entire regimen be changed from a first-line to a second-line combination in the setting of treatment failure. The new second-line regimen should involve drugs that retain activity against the patient's virus strain and should preferably include at least three new drugs, one or more of them from a new class, in order to increase the likelihood of treatment success and minimize the risk of cross-resistance.

Fig. 1 lists the second-line regimens that might be considered in adults and adolescents for the first-line regimens identified in Table B. When (d4T or ZDV) + 3TC are used as part of the first-line regimen, nucleoside cross-resistance may compromise the potency of alternative dual nucleoside components in the second-line regimen, especially in the presence of long-standing virological failure. In this situation it is necessary to make empirical alternative choices with a view to providing as much antiviral activity as possible. Given the cross-resistance that exists between d4T and ZDV, second-line regimens that might offer more activity include TDF/ddl or ABC/ddl. The issues of cost and drug hypersensitivity with ABC remain. Furthermore, high-level ZDV/3TC coresistance confers diminished susceptibility to ABC. TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but often retains activity against nucleoside-resistant viral strains. It is attractive in that, like ddl, it is administered once daily. TDF raises the level of ddl and the dose of the latter should therefore be reduced when the two drugs are given together, in order to reduce the chance of ddl-associated toxicity (e.g. neuropathy and pancreatitis).

Because of the diminished potential of almost any second-line nucleoside component, a ritonavir-enhanced PI (RTV-PI) component, i.e. lopinavir (LPV)/r, saquinavir (SQV)/r or indinavir (IDV)/r, is preferable to nelfinavir (NFV) in second-line regimens, given their potency²⁷. NFV can be considered as an alternative for the PI component if a ritonavir-enhanced PI is not available, if a cold chain is not secure or if there is a clinical contraindication to the use of another PI.

Despite being considered a potent option, IDV/r is associated with substantial renal side-effects and should also be considered as an alternative. As noted above, the role and availability of ATV/r in the developing world cannot be fully specified at present.

Fig. 1. RECOMMENDED SECOND-LINE REGIMENS IN ADULTS AND ADOLESCENTS IN THE EVENT OF TREATMENT FAILURE OF FIRST-LINE ARV REGIMENS



^a Dose of ddl should be reduced from 400 mg to 250 mg when coadministered with TDF.

^b LPV/r and SQV/r require secure cold chain. NVP can be considered as an alternative in resource-limited settings without cold chain.

For treatment failure with a first-line PI-based regimen, the choice of an alternative regimen depends on the reason for the initial choice of a PI-based, rather than an NNRTI-based, regimen. If the reason was suspected NNRTI resistance or HIV-2 infection the choice of the alternative regimen is not straightforward. In these situations the options depend on the constraints imposed by the circumstances of individual patients, the capabilities of individual managements to test for resistance to drugs, and the limited ARV formulary that may exist in particular country programmes.

Treatment failure on a triple NRTI regimen is more easily managed because two important drug classes (NNRTIs and PIs) will have been spared. Thus a RTV-PI + NNRTI +/- alternative NRTIs (e.g. ddl and/or TDF) can be considered if drug availability permits.

VIII. CONSIDERATIONS FOR SPECIFIC CATEGORIES OF PATIENTS

A. WOMEN OF CHILDBEARING POTENTIAL OR PREGNANT WOMEN

The guiding principle for the treatment of women of childbearing potential or pregnant women is that therapeutic decisions should be based solely on their need and eligibility for ART as outlined in Section III. The special circumstances of pregnancy or breast-feeding raise additional issues concerning toxicity to mothers and children, the choice of ARV drugs, and the prevention of HIV transmission from mothers to infants. These matters should be dealt with in the context of assuring optimal treatment to preserve the health of the mothers. Consequently, the recommended WHO first-line regimen for this patient subgroup is:

(d4T or ZDV) + 3TC + NVP.

The choice of ART for women with the potential to become pregnant must involve a consideration of the possibility that the ARV drugs may be received early in the first trimester, before the recognition of pregnancy and during the primary period of fetal organ development. EFV should be avoided in such women because of its potential for teratogenicity. Women who are receiving ART and do not wish to become pregnant should have effective and appropriate contraceptive methods available to them in order to reduce the likelihood of unintended pregnancy. In those women for whom effective contraception can be assured, EFV remains a viable option for the NNRTI component of the regimen. Women who are receiving ART and become pregnant should continue their treatment unless they are in the first trimester of pregnancy and EFV has been part of the regimen, in which circumstances EFV should be discontinued and replaced by NVP.

For pregnant women it may be desirable to initiate ART after the first trimester, although for such women who are severely ill the benefit of early therapy clearly outweighs any potential fetal risks, and therapy should be initiated in these cases. Additionally, the dual NRTI combination of d4T/ddI should be avoided in pregnancy and only used when no other alternatives exist, because of the potential increased risk of lactic acidosis with this combination in pregnant women.

Symptomatic NVP-associated hepatic or serious rash toxicity, although uncommon, is more frequent in women than in men and is more likely to be seen in women with comparatively elevated CD4 cell counts ($>250/\text{mm}^3$)^{41–44}. It is not known if pregnancy further predisposes women to such toxicities but cases have been reported in pregnant women^{45, 46}.

An important issue is the potential impact of NVP prophylaxis for the prevention of MTCT on the subsequent treatment of mothers and their infected infants. This question has arisen in the past two years because a single point mutation is associated with resistance for NVP. Mutations associated with NNRTI drug resistance have been detected in plasma virus in approximately 20% of women following single-dose NVP prophylaxis at six weeks postpartum; higher rates of mutant virus (67%) have been detected at six weeks postpartum where women have received two doses instead of a single intrapartum dose of NVP for the prevention of transmission^{47, 48}. Additionally, NVP resistance can develop even among women receiving additional antiretroviral drugs if they have detectable viral replication at the time of administration of single-dose NVP; genotypic NVP resistance was detected at six weeks postpartum in 15% of women who received single-dose NVP and who had received ZDV alone or combination antiretroviral drugs during pregnancy and intrapartum^{49, 50}. Resistance to 3TC is also associated with a single mutation. In a study in which 3TC was added to ZDV therapy at 32 weeks of gestation in pregnant women in France, the 3TC resistance mutation M184V was observed at six weeks postpartum in 39% of women⁵¹; 3TC resistance was also detected at one week postpartum in 12% of women receiving ZDV/3TC for four weeks for the prevention of MTCT in the PETRA study⁵². No ZDV or 3TC resistance was observed with intrapartum/one-week-postpartum ZDV/3TC in the SAINT study in South Africa^{48, 52}.

There is no information about the clinical consequences of the selection of these resistance mutations for responses to future antiretroviral therapy in women or infected infants. The mutations fade with time but doubtless remain archived in minor viral subpopulations and have the potential to re-emerge when a subsequent regimen containing NNRTI or 3TC is introduced. Studies are in progress and others are planned with a view to determining whether single-dose NVP prophylaxis compromises subsequent HAART with NNRTI-based regimens. This is one of the most pressing operational research questions in the field.

Until definitive data are available on this matter, women who have received single-dose NVP prophylaxis or 3TC prophylaxis for the prevention of MTCT should be considered eligible for NNRTI-based regimens and should not be denied access to life-sustaining therapy.

Several country programmes are already considering the use of short-course triple combination therapy for the prevention of MTCT in women who are not yet in need of treatment for their own HIV infection, and the cessation of therapy postpartum if the women do not require its continuation for their own health. The use of highly active combination therapy in such situations should prevent the emergence of resistance to the drugs and should also be highly effective in reducing perinatal HIV transmission to infants. However, this intervention also exposes both mother and fetus to potential drug toxicities in situations where therapy is not required for maternal health. Studies are in progress with a view to assessing the safety and efficacy of this approach for women and their infants, particularly for the prevention of MTCT in breast-feeding women.

When a PI-based option is preferred to an NNRTI-based regimen during pregnancy, SQV/r or NFV are reasonable choices, given the safety experience in pregnancy.

It is important to note that ARV drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. The limited data available suggest that potential drug interactions between many ARVs (particularly some NNRTIs and PIs) and hormonal contraceptives may alter safety and effectiveness of both the hormonal contraceptives and the ARVs. It is not known whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone acetate and norethisterone enantate) would be compromised, as these methods provide higher blood hormone levels than other progestogen-only hormonal contraceptives, as well as than combined oral contraceptives. Studies are underway to evaluate potential interactions between depot medroxyprogesterone acetate and selected PI and NNRTI drugs. Thus, if a woman on ARV treatment decides to initiate or continue hormonal contraceptive use, the consistent use of condoms must be recommended for preventing HIV transmission and may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

B. CHILDREN

When to start ARV therapy in infants and children

The laboratory diagnosis of HIV infection in infants aged under 18 months is difficult because of the persistence of maternal antibody. Virological tests are required in order to make definitive diagnoses of HIV infection in this age group. WHO recommendations for the initiation of ARV therapy in children are therefore divided into categories related to age and the availability of virological diagnostic tests (Table G). When CD4 cell assays are available the use of the CD4 cell percentage is recommended for decision-making on ARV treatment

rather than of the absolute CD4 cell count, because the former varies less with age (Annex B) ⁵³⁻⁵⁵. WHO strongly encourages the development of tests applicable to resource-limited settings which would allow early diagnosis of HIV infection in infants. The availability of such tests is critical to the development of improved recommendations for the initiation of therapy in infants aged under 18 months.

- ▶ For HIV-seropositive infants aged under 18 months, WHO recommends the initiation of ARV therapy in the following circumstances.
 - ▶ The infant has virologically proven infection (using either HIV DNA PCR, HIV RNA assay, or immune-complex dissociated p24 antigen) and has:
 - ▶ WHO Paediatric Stage III HIV disease (i.e. clinical AIDS) (Annex E), irrespective of CD4%; or
 - ▶ WHO Paediatric Stage II disease (Annex E), with consideration of using CD4 <20% to assist in decision-making; or
 - ▶ WHO Paediatric Stage I (i.e. asymptomatic) (Annex E) and CD4 <20% (asymptomatic children, i.e. WHO Stage I, should only be treated when there is access to CD4 assays).
 - ▶ If virological tests to confirm HIV infection status are not available but CD4 cell assays are available, WHO recommends that ARV therapy can be initiated in HIV-seropositive infants who have WHO Stage II or III disease and a CD4 percentage below 20%. In such cases, HIV antibody testing must be repeated at the age of 18 months in order to definitively confirm that the children are HIV-infected; ARV therapy should only be continued in infants with confirmed infection.
- ▶ For HIV-seropositive children aged 18 months or over, WHO recommends initiation of ARV therapy in the following circumstances.
 - ▶ WHO Paediatric Stage III HIV disease (i.e. clinical AIDS) (Annex E), irrespective of CD4 %; or
 - ▶ WHO Paediatric Stage II disease (Annex E), with consideration of using CD4 <15% to assist decision-making; or
 - ▶ WHO Paediatric Stage I (i.e. asymptomatic) (Annex E) and CD4 <15%.

It should be noted that breast-feeding infants are at risk of HIV infection during the entire period of breast-feeding, and that a negative virological or antibody test at one age does not exclude the possibility of infection occurring subsequently if breast-feeding continues.

As in HIV-infected adults, the total lymphocyte count significantly correlates with the risk of mortality in HIV-infected children^{56, 57}. The 12-month risk of mortality is >20% for children aged under 18 months with a total lymphocyte count of <2500/mm³ and for children aged 18 months or more with a total lymphocyte count of <1500/mm³. In cases where the CD4 cell count cannot be assessed, therefore, the total lymphocyte count may be used as a substitute indication for the treatment of infants or children with documented HIV infection in the presence of symptomatic disease (WHO Paediatric Stage II or III). It is preferable that an abnormal total lymphocyte count or CD4 cell count/percentage be confirmed with a second test before therapeutic decisions are made but it is recognized that this may not always be possible.

WHO recognizes that the current staging system for HIV infection in children was developed several years ago and that many of the clinical symptoms in Paediatric Stage II and III are not specific for HIV infection and may significantly overlap with those seen in children without HIV infection in resource-limited settings. Recognizing this limitation, WHO is planning a consultation with paediatric experts in order to revise the classification system in 2004. In the interim, however, the use of this WHO disease classification (Annex F) can be of value in assisting to define parameters for the initiation of therapy in resource-limited settings, although individual adaptation at the country programme level may be appropriate.

The penetration of ARVs into human breast milk in lactating women has not been quantified for most ARVs. Although some ARVs, such as nevirapine, are known to be present in breast milk, the concentration and quantity of drug ingested by infants would be less than those needed to achieve therapeutic levels. Consequently, if a breast-feeding infant is ill enough to require ARV treatment (Table G), the administration of ARVs at standard paediatric doses should be initiated regardless of whether the mother is receiving ARV therapy. Infected breast-feeding infants whose mothers are receiving ARV therapy may ingest subtherapeutic levels of some ARVs, and this could lead to the development of drug resistance in the infant's virus. It is not known whether ARVs should be administered during the breast-feeding period to infants with documented HIV infection who do not require ARV therapy themselves but whose mothers are receiving ARV treatment, and further research is needed on this matter.

TABLE G. RECOMMENDATIONS FOR INITIATING ART IN INFANTS AND CHILDREN

CD4 testing	Age	HIV diagnostic testing
<i>If CD4 testing is available</i>	< 18 months	HIV virological testing not available but infant is HIV antibody-seropositive (Note: HIV antibody test must be repeated at age 18 months to obtain definitive diagnosis of HIV infection) Positive HIV virological test ^b
	18 months	HIV antibody-seropositive
<i>If CD4 testing is not available</i>	< 18 months	HIV virological testing not available but infant HIV antibody-seropositive Positive HIV virological test
	18 months	HIV antibody-seropositive

^a A CD4 cell percentage <20% corresponds to an absolute CD4 count of approximately <1000/mm³ for children aged <12 months and <750/mm³ for children aged 12–18 months; CD4 <15% corresponds to <500/mm³ for children aged 1–5 years and to <200/mm³ for children aged >6 years.

^b HIV DNA PCR or HIV RNA amplification assays or immune complex dissociated p24 antigen assays.

^c CD4 cell percentage is advisable to assist with determining the need for immediate therapy.

^d If a child is asymptomatic and treatment is being initiated on basis of CD4 criteria, consideration should be given to performing a confirmatory CD4 assay if resources permit.

^e Many of the clinical symptoms in the WHO Paediatric Stage II and III disease classification are not specific for HIV infection and significantly overlap those seen in children without HIV infection in resource-limited settings; thus, in the absence virological testing and CD4 cell assay availability, symptomatic HIV-seropositive infants <18 months of age should only be considered for ARV therapy in exceptional circumstances (e.g. a child with a classic AIDS-defining opportunistic infection such as Kaposi's sarcoma, Pneumocystis carinii pneumonia or cryptococcal meningitis). If ARVs are given to a symptomatic HIV-seropositive infant in the absence of a definitive virological diagnosis, HIV antibody testing should be repeated at the of age 18 months to confirm infection status; ARV therapy should only be continued in infants with confirmed HIV infection.

Treatment recommendation

WHO Paediatric Stages II and III disease with CD4 <20% ^a

WHO Paediatric Stage III (i.e. AIDS) (Annex F) irrespective of CD4 %

WHO Paediatric Stage II disease (Annex F), with consideration of using CD4 <20% to assist in decision-making ^{a, c}

WHO Paediatric Stage I disease (i.e. asymptomatic) (Annex F), CD4 <20% ^{a, d}

WHO Paediatric Stage III disease, irrespective of CD4 %

WHO Paediatric Stage II disease, with consideration of using CD4 <15% to assist in decision-making, ^c

WHO Paediatric Stage I disease with CD4 <15% ^{a, d}

Treatment not recommended ^{d e}

WHO Paediatric Stage III, irrespective of total lymphocyte count

WHO Paediatric Stage II disease, with consideration of using total lymphocyte count <2500/mm³ to assist in decision-making ^f

WHO Paediatric Stage III irrespective of total lymphocyte count

WHO Paediatric Stage II disease, with consideration of using total lymphocyte count <1500/mm³ to assist in decision-making ^f

^f A total lymphocyte count of <2500/mm³ for children aged <18 months or of <1500/mm³ for children aged ≥ 18 months can be substituted for CD4% when the latter is unavailable and HIV-related symptoms exist. Its utility in asymptomatic children is unknown. In the absence of CD4 cell testing, therefore, asymptomatic HIV-infected children (WHO Paediatric Stage I) should not be treated because no other reliable marker is currently available in severely resource-constrained settings.

Recommended first-line ARV regimens in infants and children

Studies of HAART in children demonstrate that similar improvements are seen in morbidity, mortality and surrogate markers with many different potent ARV regimens^{58, 59}. Drug doses must be adjusted as a child grows in order to avoid the risk of underdosage and the development of resistance; dosing in children is therefore based on either body surface area or weight. Standardization is important so that non-expert personnel can safely dispense correct doses, and consequently it is desirable to provide health care workers with a table of drug doses that can be administered according to weight bands. Such tables may vary between localities in accordance with the availability of ARV drugs and formulations in the country concerned. In order to improve adherence, regimens chosen for children should take account of those that may be used by their parents in order to avoid different timings, and, if possible, to permit the use of the same drugs. WHO recognizes the need to provide assistance to countries in the development of such tables for training manuals so that ARV programmes can be implemented. Pending the development of a consensus on such tables in the course of 2004, samples of tables used by some paediatricians will be made available on request.

Some ARVs available for adults are also available in formulations specifically designed for children. However, formulations appropriate for use by young children who cannot swallow whole tablets or capsules are not widely available in resource-limited settings. For some ARVs, capsules and tablets are available in sufficiently low doses to enable accurate dosing for children (e.g. d4T capsules of 15, 20 and 30 mg, or NFV scored tablets that can be halved and crushed), and the pharmacokinetics of crushed tablets or sprinkled capsule contents in children have been evaluated. However, many drugs do not have solid formulations in doses appropriate for paediatric use and some solid formulations do not have all drug components evenly distributed in the tablets (e.g. fixed-dose ZDV/3TC). The use of tablets that require cutting up, particularly unscored tablets, can result in the underdosing or overdosing of children, which can lead to an increased risk of resistance or toxicity. Moreover, the doses cannot easily be adjusted as the children grow. However, WHO recognizes that until appropriate formulations can be made more widely available the splitting of adult-dose solid formulation ARVs, while suboptimal, may be the only way a severely ill child can receive therapy, and should be considered when no alternatives are available. Health care providers should be aware that current fixed-dose combination formulations may not contain the appropriate doses of each of the component drugs for children on a weight basis. This is a specific problem for the NVP component of the fixed-dose formulation of ZDV/3TC/NVP, for which additional NVP may be necessary if tablets are used to treat younger children (Annex F). WHO strongly encourages the development of formulations

appropriate for paediatric use, particularly solid formulations in doses that can be used by paediatric patients (e.g. crushable tablets or openable capsules), as liquid formulations may have a more limited shelf-life than solid formulations, they may be more expensive, they may be difficult to store and they may require the use of syringes for accurate administration.

The preferred first-line treatment option for children includes (d4T or ZDV) + 3TC plus an NNRTI (NVP or EFV) (Table H), for the same reasons as discussed for adult initial ARV regimens. A caveat is that EFV cannot be used currently in children under 3 years of age because of a lack of appropriate formulation and dosing information, although these matters are under study. Consequently, for children aged under 3 years or weighing under 10 kg, NVP should be the NNRTI of choice. The use of ZDV/3TC/ABC as first-line therapy is now considered a secondary alternative because of the results obtained with ACTG A5095 in adults (see Section IV); further data are awaited.

EFV would be the NNRTI of choice for children who require ARV therapy but need or are receiving anti-TB therapy containing rifampicin. For children under 3 years of age who require ARV therapy while receiving anti-TB therapy, the use of ZDV/3TC/ABC should be considered while the TB therapy is being administered, as SQV/r is not available in a formulation that is appropriate for children of this age. Monitoring for possible ABC hypersensitivity should be assured. SQV/r may also be considered for older children who can receive adult doses of the drugs (i.e. children weighing ≥ 25 kg).

TABLE H. RECOMMENDED FIRST-LINE ARV REGIMENS FOR INFANTS AND CHILDREN

First-line regimen	Comment
d4T or ZDV	
<i>plus</i> 3TC	
<i>plus</i> NVP or EFV	NNRTI choice: <ul style="list-style-type: none"> • If age < 3 years or weight < 10 kg, NVP • If age > 3 years or weight > 10 kg, NVP or EFV

If a mother has received ARV during pregnancy, either to reduce MTCT or for her own disease, there is a possibility that the baby may become infected with drug-resistant virus. Additionally, resistance could be induced de novo in an infected infant who is exposed to an ARV drug being used for prophylaxis before the infection status of the infant is known. This is a particular problem

if NVP or 3TC has been used, either alone or as a component of a two-drug regimen, for prophylaxis of MTCT, because a single point mutation is associated with resistance to these two drugs ^{47, 51}. Following single-dose NVP, 46% of infants have NNRTI-associated mutations (primarily the Y181C mutation, which may not always be associated with cross-resistance to EFV). As has been observed in mothers, these mutations fade with time but probably remain as minor viral subpopulations ⁴⁷. It is not known whether ARV choices should be modified for infants who have been exposed to ARVs used for the prevention of MTCT. Studies in children are in progress or are planned, as they are in mothers, to investigate whether single-dose NVP prophylaxis compromises subsequent HAART with NNRTI-based regimens. WHO recognizes the urgency of such research. However, until there are data allowing these questions to be definitively answered, children who require ARV therapy and who have previously received single-dose NVP or 3TC as part of MCTC prophylaxis should be considered eligible for NNRTI-based regimens and should not be denied access to life-sustaining therapy.

Clinical assessment of infants and children receiving ARV therapy
Important clinical signs of response to ARV therapy in children include: improvement in growth in children who have been failing to grow; improvement in neurological symptoms and development in children who have been demonstrating delay in the achievement of developmental milestones or encephalopathy; and/or decreased frequency of infections (bacterial infections, oral thrush, and/or other opportunistic infections).

Laboratory assessments for children on ARV therapy are the same as those recommended for adults (Table G). In addition to the clinical assessments recommended for adults, the clinical monitoring of ARV treatment in children should cover:

- ▶ nutrition and nutritional status;
- ▶ weight and height growth;
- ▶ developmental milestones;
- ▶ neurological symptoms.

Reasons for changing ARV therapy in infants and children

The principles on which to base changes in therapy for children are similar to those applied for adults, and the management of drug toxicity is the same. If toxicity is related to an identifiable drug in the regimen, the offending drug can be replaced with one that does not have the same side-effects. In children, important clinical signs of drug failure include: a lack of growth in children who

show an initial response to treatment, or a decline in growth among children who show an initial growth response to therapy; a loss of neurodevelopment milestones or the development of encephalopathy; and the recurrence of infections, such as oral candidiasis that is refractory to treatment^{60–63} (Table I). It should not be concluded, on the basis of clinical criteria, that an ARV regimen is failing until the child in question has had a reasonable trial on the therapy (e.g. the child should have received the regimen for at least 24 weeks).

Because of age-related declines in CD4 absolute cell counts until the age of 6 years, when near-adult levels are reached, it is difficult to use such counts for assessing therapy failure in younger children. However, for children aged 6 years or more, similar CD4 cell count criteria to those used for adults are appropriate (Table E). Because the CD4 cell percentage varies less with age it can be used to gauge treatment response regardless of age. No data are available on the use of total lymphocyte counts for the evaluation of response to ARV therapy.

TABLE I. CLINICAL AND CD4 COUNT DEFINITIONS OF TREATMENT FAILURE IN INFANTS AND CHILDREN

Clinical signs of treatment failure	CD4 cell criteria for treatment failure ^a
<ul style="list-style-type: none"> Lack of growth among children who show an initial response to treatment, or decline in growth among children who show an initial growth response to therapy. 	<ul style="list-style-type: none"> Return of CD4 cell percentage (or for children >6 years of age, of absolute CD4 cell count) to pretherapy baseline or below, in absence of other concurrent infection explaining transient CD4 decrease.
<ul style="list-style-type: none"> Loss of neurodevelopmental milestones or development of encephalopathy. 	<ul style="list-style-type: none"> 50% fall from peak level on therapy of CD4 cell percentage (or for children >6 years of age, of absolute CD4 cell count) in absence of other concurrent infection explaining transient CD4 decrease.
<ul style="list-style-type: none"> Occurrence of new opportunistic infection or malignancy signifying clinical disease progression.^b 	
<ul style="list-style-type: none"> Recurrence of prior opportunistic infections, such as oral candidiasis that is refractory to treatment. 	

^a If a child is asymptomatic and treatment failure is being defined by CD4 cell criteria alone, consideration should be given to performing a confirmatory CD4 count if resources permit.

^b This must be distinguished from immune reconstitution syndrome, which can occur in the first three months following the initiation of HAART and does not signify treatment failure.

Recommended second-line ARV therapy for infants and children

Second-line therapy for children in the event of failure of a first-line regimen includes a change in the nucleoside backbone, in accordance with the same principles as are applied for adults (e.g. from ZDV + 3TC to ABC + ddI), plus a protease inhibitor (Table J). The use of PIs other than LPV/r and NFV is more problematic in children because of a lack of suitable paediatric drug formulations for IDV and SQV and a lack of appropriate dosing information for ritonavir-boosted PIs other than LPV/r. However, the use of SQV/r can be considered as an alternative for children who are able to swallow capsules and who weigh 25 kg or more, and can therefore receive the adult dosage. TDF cannot be recommended for paediatric treatment at present because of limited data on appropriate dosing for children, particularly those aged under 8 years, and because of questions about bone toxicity, which may be of more concern and/or more frequent in growing children than in adults.

TABLE J. RECOMMENDED ARV REGIMENS FOR INFANTS AND CHILDREN WITH TREATMENT FAILURE

First-line regimen	Second-line regimen
d4T or ZDV	ABC
<i>plus</i>	<i>plus</i>
3TC	ddI
<i>plus</i>	<i>plus</i>
NNRTI:	Protease inhibitor:
NVP or EFV	LPV/r or NFV, or SQV/r if weight ≥ 25 kg

C. PEOPLE WITH TUBERCULOSIS DISEASE AND HIV COINFECTION

Tuberculosis is an entry point for a significant proportion of patients eligible for ART. ART is recommended for all patients with TB who have CD4 counts below 200 cells/mm³, and should be considered for patients with CD4 counts below 350 cells/mm³. In the absence of CD4 cell counts, ART is recommended for all patients with TB. It is acknowledged that this will result in the treatment of individuals with CD4 cell counts over 350 who otherwise would not receive ART. The treatment of TB remains a central priority for patient management and should not be compromised by ART^{64–67}.

Patients with TB merit special consideration because comanagement of HIV and TB is complicated by rifampicin drug interactions with NNRTIs and PIs,

pill burden, adherence and drug toxicity. Data supporting specific treatment recommendations are incomplete and research is urgently needed in this area^{68–71}. Taking the available data into account, the first-line treatment recommendation for patients with TB and HIV coinfection is (ZDV or d4T) + 3TC + EFV (600 or 800 mg/day). The 800-mg dose of EFV achieves higher drug levels than those seen in the absence of rifampicin and thus may reduce the chance of HIV drug resistance. However, it can also increase the toxicity risk. SQV/RTV 400/400 mg bid, SQV/r 1600/200 mg qd (in soft gel formulation – sgc) or LPV/RTV 400/400 mg bid in combination with the NRTI backbone are alternatives to EFV, although tolerability, clinical monitoring and risk of resistance may be problematic. Endorsement of these PI-based regimens requires further data. ABC is another alternative to EFV with the advantages of low pill burden, no interaction with rifampicin, and suitability for administration to children weighing 25 kg or less, for whom appropriate EFV dosing information is not yet available. Concerns about this regimen include ones relating to monitoring for hypersensitivity syndrome and virological potency. Data on the use of NVP + rifampicin are limited and conflicting. NVP levels are reduced in the presence of rifampicin, and higher NVP doses have not been evaluated. Although some clinical experience reports adequate viral and immunological response and acceptable toxicity, this regimen should only be considered when no other options are available. For women of childbearing age (without effective contraception), pregnant women, and children with TB, either SQV/r or ABC + (d4T or ZDV) + 3TC is recommended. For children weighing 25 kg or less, (d4T or ZDV)/3TC/ABC is recommended as an alternative^{72–79}.

The optimal time to initiate ART in patients with TB is not known. Case-fatality rates in many patients with TB during the first two months of TB treatment are high, particularly when they present with advanced HIV disease, and ART in this setting might be life-saving. On the other hand, pill burden, drug-to-drug interaction, potential toxicity and immune reconstitution syndrome should be kept in mind when deciding on the best time to begin treatment^{68, 69, 80, 81}. The management of patients with HIV and TB poses many challenges, including that of achieving patient acceptance of both diagnoses. Pending current studies, WHO recommends that ART in patients with CD4 cell counts below 200/mm³ be started between two weeks and two months after the start of TB therapy, when the patient has stabilized on this therapy. This provisional recommendation is meant to encourage rapid initiation of therapy in patients among whom there may be a high mortality rate. However, deferring the start of ART may be reasonable in a variety of clinical scenarios. For example, in patients with higher CD4 cell counts the commencement of ART may be delayed until after the induction phase of TB therapy is completed in order to simplify the management of treatment.

TABLE L. ART RECOMMENDATIONS FOR INDIVIDUALS WITH TB DISEASE AND HIV COINFECTION

CD4 cell count	Recommended regimen	Comments
CD4 <200 mm ³	Start TB treatment. Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months) ^a : EFV-containing regimens ^{b, c, d} .	Recommend ART. EFV is contraindicated in pregnant women or women of childbearing potential without effective contraception.
CD4 200–350/mm ³	Start TB treatment. Start one of the regimens below after the initiation phase (start earlier if severely compromised): EFV-containing regimens b or NVP-containing regimens in case of rifampicin-free continuation phase TB treatment regimen.	Consider ART.
CD4 >350 mm ³	Start TB treatment.	Defer ART ^e .
CD4 not available	Start TB treatment.	Consider ART ^{a, f}

^a Timing of ART initiation should be based on clinical judgement in relation to other signs of immunodeficiency (Table A). For extrapulmonary TB, ART should be started as soon as TB treatment is tolerated, irrespective of CD4 cell count

^b Alternatives to the EFV portion of the regimen include: SQV/RTV (400/400 mg bid), SQV/r (1600/200 mg qd in sgc), LPV/RTV (400/400 mg bid) and ABC.

^c NVP (200 mg qd for two weeks followed by 200 mg bid) may be used in place of EFV in absence of other options. NVP-containing regimens include: d4T/3TC/NVP or ZDV/3TC/NVP.

^d EFV-containing regimens include d4T/3TC/EFV and ZDV/3TC/EFV.

^e Unless non-TB Stage IV conditions are present (Table A). Otherwise start ART upon completion of TB treatment.

^f If no other signs of immunodeficiency are present and patient is improving on TB treatment, ART should be started upon completion of TB treatment.

D. INJECTING DRUG USERS

The clinical and immunological criteria for initiating HAART in substance-dependent patients do not differ from those in the general recommendations. Injecting drug users who are eligible for ART should therefore be guaranteed access to this life-saving therapy. Special considerations for this population include dealing prospectively with lifestyle instability that challenges drug adherence and accounting for the potential drug interactions of ARVs with agents such as methadone. The development of programmes which integrate care of drug dependence (including drug substitution therapy) and HIV is encouraged. In such settings, approaches such as directly observed therapy can be implemented. Once-daily ARV regimens are being intensively explored in this arena and lend themselves to such approaches. The number of ARVs approved or being investigated for once-daily use is steadily increasing. They include 3TC, FTC, ddI, d4T, TDF, ABC, EFV, SQV/r, LPV/r and ATV.

The coadministration of methadone with EFV, NVP or RTV in HIV-infected individuals with a history of injecting drug use resulted in decreased plasma levels of methadone and signs of opiate withdrawal. Patients should be monitored for signs of withdrawal and their methadone dose should be increased in appropriate increments over time so as to alleviate withdrawal symptoms. An important option can thus be provided for treatment programmes directed at this vulnerable population.

IX. ADHERENCE TO ANTIRETROVIRAL THERAPY

Adherence to ART is well recognized to be an essential component of individual and programmatic treatment success^{11, 14, 17, 23, 28, 33, 47, 48, 51, 56, 60, 65, 82}. Studies of drug adherence in the developed world have suggested that higher levels of drug adherence are associated with improved virological and clinical outcomes and that rates exceeding 95% are desirable in order to maximize the benefits of ART. It is difficult to achieve rates this high over a long period of time. Numerous approaches to improving adherence have been investigated in the developed world and have begun to be explored in the developing world. Viral load testing will not be widely introduced in the developing world in the near future because of cost and technical considerations. Consequently, it is particularly important to focus on maximizing adherence in order to try to avoid drug resistance and ensure the durability of effect of ARV regimens.

The proper education of patients before the initiation of therapy is vital for the success of adherence strategies. Such education should cover basic information about HIV and its manifestations, the benefits and side-effects of ARV medications, how the medications should be taken and the importance of not missing any doses. Peer counsellors and visual materials can be particularly useful in this process. Keys to success once treatment has begun include trying to minimize the number of pills (in part through the use of FDCs), the packaging of pills (coblister packs when available), the frequency of dosing (no more than twice-daily regimens), avoidance of food precautions, fitting the ARVs into the patient's lifestyle, and the involvement of relatives, friends and/or community members in support of the patient's adherence.

After the initiation of therapy it is essential to maintain support for adherence. This should involve adherence assessments whenever there is a visit to a health centre, reinforcement of adherence principles to the patient by treatment supporters, and the continuous involvement of relatives, friends and/or community support personnel. Although the penetration of ART in the developing world has been low in relation to the burden of disease, important lessons have been learnt which can be incorporated into newly developing or expanding programmes. These lessons relate to the following measures.

- ▶ Provision of medications free of charge through subsidization or other financing strategies for people who can least afford treatment. It has been suggested that cost-sharing may assist adherence, although experiences can be expected to vary between countries. Recent data from Senegal and other African countries indicates that cost-sharing is detrimental to long-term adherence. These issues need further exploration^{83, 84}.
- ▶ Engagement of family or community members in adherence education and maintenance programmes. Home visits can be particularly useful. Minimizing stigma through psychosocial support is essential.
- ▶ Family-based care when more than one family member is HI- infected. This is particularly important when both mother and child are infected.
- ▶ Use of pillboxes or blister packs.
- ▶ Directly observed therapy (DOT) or modified DOT programmes. This approach is resource-intensive and difficult to introduce on a large scale and for the lifelong duration of ART. However, it may be helpful for certain groups and for early patient training.
- ▶ Use of mobile vans to reach rural communities.
- ▶ At the programmatic level it is essential to ensure proper stock and storage of ARVs and the provision of necessary resources for culturally appropriate adherence programmes.

Adherence may be more difficult in pregnant women and immediately postpartum women than in non-pregnant individuals. Pregnancy-associated morning sickness and gastrointestinal upset may complicate ART and the situation may be exacerbated by ARV-associated side-effects or concern about the potential effects of drugs on the fetus. In the postpartum period, physical changes and the demands of caring for a neonate may compromise maternal drug adherence. Specific, culturally appropriate adherence supports should be developed at the country level in order to address the special problems associated with pregnant and postpartum women.

Adherence in children is a special challenge, particularly if the family unit is disrupted as a consequence of adverse health or economic conditions. Family-based HIV care programmes are one of the best approaches to ensuring children's health. Moreover, it is imperative that paediatric formulations be improved and made widely available. Where possible they should match the adult regimens so that that family-based care can be pursued effectively and so that children can be properly dosed.

X. DRUG RESISTANCE SURVEILLANCE

ARV drug resistance is a major challenge to treatment programmes for both developed and developing countries. Currently, approximately 10% of new HIV-1 infections in the USA and Europe involve viral strains exhibiting resistance to at least one drug. Scale-up programmes in the developing world can take advantage of the lessons learnt in developed countries through proper initiation of potent regimens, incorporation of culturally appropriate adherence training and maintenance programmes, and synchronization with drug resistance surveillance and monitoring initiatives.

Drug resistance genotyping is not on the near-term or mid-term horizon for individual patient management in resource-limited settings but country programmes are encouraged to develop or participate in drug resistance surveillance and monitoring programmes to assist with planning at the population level. This may involve developing or expanding genotypic capabilities at regional or national centres of excellence. Such capabilities can be considered an important public health tool that can be used to inform national, regional and global ARV scale-up programmes concerning trends in the prevalence of drug resistance so that decisions can be made to minimize its impact.

WHO recommends that countries planning to implement ART programmes should concurrently introduce HIV drug resistance sentinel surveillance systems. This will allow countries to detect potential drug resistance at the population level and to modify recommended treatment regimens accordingly. Initially, treatment-naïve persons should be surveyed in order to establish prevalence rates of drug resistance in the infected population, and treatment-experienced persons should be monitored, particularly those diagnosed with their first episode of treatment failure. A Global HIV Drug Resistance Surveillance and Monitoring Network is being established by WHO in collaboration with partner organizations with a view to assisting Member States in this arena⁸².

XI. CONCLUSIONS

Member States of WHO face both a great challenge and a great opportunity. The world community can confront the AIDS pandemic in developing countries with ART, the most effective life-sustaining tool in the HIV care package. The current nexus of political commitment, new sources of funding, ARV availability and lower drug prices have created this opportunity. WHO is committed to assisting resource-limited countries with the scale-up of ART through its comprehensive 3-by-5 Plan. The present updated ARV treatment guidelines are intended to help national programmes to provide ARV access for all infected adults and children in need of treatment.

ANNEX A. DOSAGES OF ANTIRETROVIRAL DRUGS FOR ADULTS AND ADOLESCENTS

Drug class/drug	Dose a
Nucleoside RTIs	
Abacavir (ABC)	300 mg twice daily
Didanosine (ddl)	400 mg once daily (250 mg once daily if <60 kg) (250 mg once daily if administered with TDF)
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	40 mg twice daily (30 mg twice daily if <60 kg)
Zidovudine (ZDV)	300 mg twice daily
Nucleotide RTI	
Tenofovir (TDF)	300 mg once daily (Note: drug interaction with ddl necessitates dose reduction of latter)
Non-nucleoside RTIs	
Efavirenz (EFV)	600 mg once daily ^b
Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily
Protease inhibitors	
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily ^{c, d}
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily (533 mg/133 mg twice daily when combined with EFV or NVP)
Nelfinavir (NFV)	1250 mg twice daily
Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg twice daily or 1600 mg/200 mg once daily ^{d, e}

^a These dosages are in common clinical use. The dosages featured in this table were selected on the basis of the best available clinical evidence. Dosages that can be given once daily or twice daily were preferred in order to enhance adherence to therapy. The doses listed are those for individuals with normal renal and hepatic function. Product-specific information should be consulted for dose adjustments that may be indicated with renal or hepatic dysfunction or for potential drug interactions with other HIV and non-HIV medications.

^b See TB section for specific TB dosing.

^c This dosage regimen is in common clinical use. Other IDV/r dosage regimens that range from 800 mg/200 mg bid to 400 mg/100 mg bid are also in clinical use.

^d Dosage adjustment when combined with an NNRTI is indicated but a formal recommendation cannot be made at this time. One consideration is to increase the RTV component to 200 mg bid when EFV or NVP is used concomitantly. More drug interaction data are needed.

^e Both the hard-gel and soft-gel capsule formulations can be used when SQV is combined with RTV.

Annex B. HUMAN IMMUNODEFICIENCY VIRUS PAEDIATRIC IMMUNE CATEGORY CLASSIFICATION SYSTEM BASED ON AGE-SPECIFIC CD4⁺ T CELL COUNT AND PERCENTAGE

Modified from: Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43(No. RR-12):1-10.

Immune category	<12 months		1–5 years		6–12 years	
	No./mm ³	%	No./mm ³	%	No./mm ³	%
Category 1: No suppression	1500	25%	1000	25%	500	25%
Category 2: Moderate suppression	750–1499	15%–24%	500–999	15%–24%	200–499	15%–24%
Category 3: Severe suppression	<750	<15%	<500	<15%	<200	<15%

Annex C. SUMMARY OF PAEDIATRIC DRUG FORMULATIONS AND DOSES

Name of drug	Formulations	Pharmaco-kinetic data available
<i>Nucleoside analogue reverse transcriptase inhibitors</i>		
Zidovudine (ZDV)	Syrup: 10 mg/ml Capsules: 100 mg; 250 mg Tablet: 300 mg	All ages
Lamivudine (3TC)	Oral solution: 10 mg/ml Tablet: 150 mg	All ages
Fixed-dose combination of ZDV plus 3TC	No liquid available Tablet: 300 mg ZDV plus 150 mg 3TC	Adolescents and adults

Age (weight), dose and dose frequency	Other comments
<p><4 weeks: 4 mg/kg/dose twice daily</p> <p>4 weeks to 13 years: 180 mg/m²/dose twice daily a</p> <p>Maximum dose: 3 years: 300 mg/dose twice daily</p>	<p>Large volume of syrup not well tolerated in older children</p> <p>Syrup needs storage in glass jars and is light-sensitive</p> <p>Can be given with food</p> <p>Doses of 600 mg/m²/dose per day required for HIV encephalopathy</p> <p>Capsule can be opened and contents dispersed or tablet crushed and contents mixed with small amount of water or food and immediately taken (solution is stable at room temperature)</p> <p>Do not use with d4T (antagonistic antiretroviral effect)</p>
<p><30 days: 2 mg/kg/dose twice daily</p> <p>30 days or <60 kg: 4 mg/kg/dose twice daily</p> <p>Maximum dose: >60 kg: 150 mg/dose twice daily</p>	<p>Well tolerated</p> <p>Can be given with food</p> <p>Store solution at room temperature (use within one month of opening)</p> <p>Tablet can be crushed and contents mixed with small amount water or food and immediately taken</p>
<p>Maximum dose: >13 years or >60 kg: 1 tablet/dose twice daily</p> <p>(should not be given if weight <30 kg)</p>	<p>Preferably, tablet should not be split</p> <p>Tablet can be crushed and contents mixed with small amount of water or food and immediately taken</p> <p>At weight <30 kg, ZDV and 3TC cannot be dosed accurately in tablet form</p>

Stavudine (d4T)	<p>Oral solution: 1 mg/ml</p> <p>Capsules: 15 mg, 20 mg, 30 mg, 40 mg</p>	All ages
Fixed-dose combination of d4T plus 3TC	<p>No liquid available</p> <p>Tablet: d4T 30 mg plus 3TC 150 mg; d4T 40 mg plus 3TC 150 mg</p>	Adolescents and adults
Didanosine (ddl, dideoxyinosine)	<p>Oral suspension paediatric powder/ water: 10 mg/ml; in many countries needs to be made up with additional antacid</p> <p>Chewable tablets: 25 mg; 50 mg; 100 mg; 150 mg; 200 mg</p> <p>Enteric-coated beadlets in capsules: 125 mg; 200 mg; 250 mg; 400 mg</p>	All ages
Abacavir (ABC)	<p>Oral solution: 20 mg/ml</p> <p>Tablet: 300 mg</p>	Over age of 3 months

<p><30 kg: 1 mg/kg/dose twice daily</p> <p>30 to 60 kg: 30 mg/dose twice daily</p> <p>Maximum dose: >60 kg: 40 mg/dose twice daily</p>	<p>Large volume of solution</p> <p>Keep solution refrigerated; stable for 30 days; must be well shaken and stored in glass bottles</p> <p>Capsules can be opened and mixed with small amount of food or water (stable in solution for 24 hours if kept refrigerated)</p> <p>Do not use with AZT (antagonistic antiretroviral effect)</p>
<p>Maximum dose: 30–60 kg: one 30-mg d4T-based tablet twice daily</p> <p>≥60 kg: one 40-mg d4T-based tablet twice daily</p>	<p>Preferably, tablet should not be split</p> <p>See comments under individual drug components</p>
<p><3 months: 50 mg/m²/dose twice daily</p> <p>3 months to <13 years: 90–120 mg/m²/dose twice daily or 240 mg/m²/dose once daily</p> <p>Maximum dose: 13 years or >60 kg: 200 mg/dose twice daily or 400 mg once daily</p>	<p>Keep suspension refrigerated; stable for 30 days; must be well shaken</p> <p>Administer on empty stomach, at least 30 minutes before or 2 hours after eating</p> <p>If tablets dispersed in water, at least 2 tablets of appropriate strength should be dissolved for adequate buffering</p> <p>Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food</p>
<p><16 years or <37.5 kg: 8 mg/kg/dose twice daily</p> <p>Maximum dose: >16 years or >37.5 kg: 300 mg/dose twice daily</p>	<p>Can be given with food</p> <p>Tablet can be crushed and contents mixed with small amount water or food and immediately ingested</p> <p>PARENTS MUST BE WARNED ABOUT HYPERSENSITIVITY REACTION</p> <p>ABC should be stopped permanently if hypersensitivity reaction occurs</p>

Fixed-dose combination of ZDV plus 3TC plus ABC	No liquid available Tablet: ZDV 300 mg plus 3TC 150 mg plus ABC 300 mg	Adolescents and adults
<i>Non-nucleoside reverse transcriptase inhibitors</i>		
Nevirapine (NVP)	Oral suspension: 10 mg/ml Tablet: 200 mg	All ages

<p>Maximum dose: >40 kg: 1 tablet/dose twice daily</p>	<p>Preferably, tablet should not be split</p> <p>At weight <30 kg, ZDV/3TC/ABC cannot be dosed accurately in tablet form</p> <p>MUST WARN PARENTS ABOUT HYPERSENSITIVITY REACTION.</p> <p>ZDV/3TC/ABC should be stopped permanently if hypersensitivity reaction occurs</p>
<p>15 to 30 days: 5 mg/kg/dose once daily x 2 weeks, then 120 mg/m²/dose twice daily x 2 weeks, then 200 mg/m²/dose twice daily ^a</p> <p>>30 days to 13 years: 120 mg/m²/dose once daily for 2 weeks, then 120–200 mg/m²/dose twice daily ^a</p> <p>Maximum dose: >13 yrs: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily</p>	<p>If rifampicin coadministration, avoid use (see TB section)</p> <p>Store suspension at room temperature; must be well shaken</p> <p>Can be given with food</p> <p>Tablets are scored and can be divided into two equal parts to give a 100 mg dose; can be crushed and combined with a small amount of water or food and immediately administered</p> <p>PARENTS MUST BE WARNED ABOUT RASH. Do not escalate dose if rash occurs (if mild/moderate rash, hold drug; when rash has cleared, restart dosing from beginning of dose escalation; if severe rash, discontinue drug)</p> <p>Drug interactions</p>

Efavirenz (EFV)	<p>Syrup: 30 mg/ml (note: syrup requires higher doses than capsules; see dosing chart)</p> <p>Capsules: 50 mg, 100 mg, 200 mg</p>	Only for children over 3 years of age
Fixed-dose combination of d4T plus 3TC plus NVP	<p>No liquid available</p> <p>Tablet: 30 mg d4T/150 mg 3TC/200 mg NVP; 40 mg d4T/150 mg 3TC/200 mg NVP</p>	Adults and adolescents

<p>Capsule (liquid) dose for >3 years: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily</p> <p>15 to <20 kg: 250 mg (300 mg = 10 ml) once daily</p> <p>20 to <25 kg: 300 mg (360 mg = 12 ml) once daily</p> <p>25 to <33 kg: 350 mg (450 mg = 15 ml) once daily</p> <p>33 to <40 kg: 400 mg (510 mg = 17 ml) once daily</p> <p>Maximum dose: 40 kg: 600 mg once daily</p>	<p>Capsules may be opened and added to food but have very peppery taste; however, can be mixed with sweet foods or jam to disguise taste</p> <p>Can be given with food (but avoid after high-fat meals, which increase absorption by 50%); best given at bedtime, especially first 2 weeks, to reduce CNS side-effects.</p> <p>Drug interactions</p>
<p>Maximum dose: 30–60 kg: one 30 mg d4T-based tablet twice daily</p> <p>60 kg: one 40 mg d4T-based tablet twice daily</p>	<p>Preferably, tablet should not be split</p> <p>At weight <30 kg, d4T/3TC/NVP cannot be dosed accurately in tablet form; if tablets are split, NVP dose requirements will be inadequate for very young children and additional NVP is needed to give total of 200 mg/m²/dose twice daily Contains NVP, therefore dose escalation required (see NVP dosing recommendations) See comments under individual drug components</p>

<i>Protease inhibitors</i>		
Nelfinavir (NFV)	<p>Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25 ml scoop): 5 ml</p> <p>Tablet: 250 mg (tablets can be halved; can be crushed and added to food or dissolved in water)</p>	<p>All ages</p> <p>However, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants <1 year</p>
Lopinavir/ritonavir, (LPV/r)	<p>Oral solution: 80mg/ml lopinavir plus 20 mg/ml ritonavir</p> <p>Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir</p>	<p>6 months of age or older</p>

^a Metre² body surface area calculation: square root of (height in centimetres times weight in kilograms divided by 3600).

<p><1 year: 50 mg/kg/dose three times daily or 75 mg/kg/dose twice daily</p> <p>>1 year to <13 years: 55 to 65 mg/kg/ dose twice daily</p> <p>Maximum dose: 13 years: 1250 mg/dose twice daily</p>	<p>Powder is sweet, faintly bitter but gritty and hard to dissolve; must be reconstituted immediately before administration in water, milk, formula, pudding, etc.; do not use acidic food or juice (which increase bitter taste); solution stable for 6 hours</p> <p>Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given</p> <p>Powder and tablets can be stored at room temperature</p> <p>Take with food</p> <p>Drug interactions (less than ritonavir-containing protease inhibitors)</p>
<p>>6 months to 13 years: 225 mg/m² LPV/ 57.5 mg/m² ritonavir twice daily ^a or weight-based dosing:</p> <p>7–15 kg: 12mg/kg LPV/3 mg/kg ritonavir/ dose twice daily</p> <p>15–40 kg: 10 mg/kg lopinavir/5 mg/kg ritonavir twice daily</p> <p>Maximum dose: >40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml) twice daily</p>	<p>Preferably, oral solution and capsules should be refrigerated; however, can be stored at room temperature up to 25 °C (77 °F) for 2 months; at temperature >25 °C (77 °F) the drug degrades more rapidly</p> <p>Liquid formulation has low volume but bitter taste</p> <p>Capsules large</p> <p>Capsules should not be crushed or opened but must be swallowed whole</p> <p>Should be taken with food</p> <p>Drug interactions</p>

Annex D. FIXED-DOSE COMBINATIONS OF ARVs AVAILABLE ON 1 DECEMBER 2003

Three-drug fixed-dose combinations	d4T (40 mg) + 3TC (150 mg) + NVP (200 mg)
	d4T (30 mg) + 3TC (150 mg) + NVP (200 mg)
	ZDV (300 mg) + 3TC (150 mg) + ABC (300 mg)
	ZDV (300 mg) + 3TC (150 mg) + NVP (200 mg)
Two-drug fixed-dose combinations	d4T (30 mg) + 3TC (150 mg)
	d4T (40 mg) + 3TC (150 mg)
	ZDV (300 mg) + 3TC (150 mg)

Note: WHO encourages the use of fixed-dose combinations when formulations of assured quality and proven bioequivalence are available and offer operational advantages. Not all the FDCs in this table have been evaluated for prequalification by WHO. WHO operates a voluntary prequalification system, in which, as of 1 December 2003, three manufacturers prequalified ZDV/3TC combinations, two prequalified d4T/3TC/NVP combinations, and one prequalified ZDV/3TC/ABC. The list of WHO-prequalified manufacturers is continuously updated and is available at: <http://www.who.int/medicines>

Annex E. WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS

Clinical Stage I

1. Asymptomatic
2. Generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Clinical Stage II

3. Weight loss <10% of body weight
4. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
5. Herpes zoster within the last five years
6. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)

And/or performance scale 2: symptomatic, normal activity

Clinical Stage III

7. Weight loss >10% of body weight
8. Unexplained chronic diarrhoea, >1 month
9. Unexplained prolonged fever (intermittent or constant), >1 month
10. Oral candidiasis (thrush)
11. Oral hairy leucoplakia
12. Pulmonary tuberculosis
13. Severe bacterial infections (i.e. pneumonia, pyomyositis)

And/or performance scale 3: bedridden <50% of the day during last month

Clinical Stage IV:

14. HIV wasting syndrome ^a
15. Pneumocystic carinii pneumonia
16. Toxoplasmosis of the brain
17. Cryptosporidiosis with diarrhoea >1 month
18. Cryptococcosis, extrapulmonary
19. Cytomegalovirus disease of an organ other than liver, spleen or lymph node (e.g. retinitis)
20. Herpes simplex virus infection, mucocutaneous (>1month) or visceral
21. Progressive multifocal leucoencephalopathy
22. Any disseminated endemic mycosis
23. Candidiasis of oesophagus, trachea, bronchi
24. Atypical mycobacteriosis, disseminated or pulmonary
25. Non-typhoid Salmonella septicaemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma
29. HIV encephalopathy ^b

And/or performance scale 4: bedridden >50% of the day during last month

^a HIV wasting syndrome: weight loss of >10% of body weight, plus either unexplained chronic diarrhoea (>1 month) or chronic weakness and unexplained prolonged fever (>1 month).

^b HIV encephalopathy: clinical findings of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition, other than HIV infection, which could explain the findings.

Annex F. WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN CHILDREN

Clinical Stage I:

1. Asymptomatic
2. Generalized lymphadenopathy

Clinical Stage II:

3. Chronic diarrhoea >30 days duration in absence of known etiology
4. Severe persistent or recurrent candidiasis outside the neonatal period
5. Weight loss or failure to thrive in the absence of known etiology
6. Persistent fever >30 days duration in the absence of known etiology
7. Recurrent severe bacterial infections other than septicaemia or meningitis (e.g. osteomyelitis, bacterial (non-TB) pneumonia, abscesses)

Clinical Stage III:

8. AIDS-defining opportunistic infections
9. Severe failure to thrive (wasting) in the absence of known etiology ^a
10. Progressive encephalopathy
11. Malignancy
12. Recurrent septicaemia or meningitis

^a Persistent weight loss >10% of baseline or less than 5th percentile on weight for height chart on 2 consecutive measurements more than 1 month apart in the absence of another etiology or concurrent illness.

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