SCALING UP ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS

GUIDELINES FOR A PUBLIC HEALTH APPROACH

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SCALING UP ANTIRETROVIRAL THERAPY IN RESOURCE-LIMITED SETTINGS

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
AIDS	acquired immunodeficiency syndrome
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral
AUC	area under the curve
AZT	zidovudine
CNS	central nervous system
d4T	stavudine
ddC	zalcitabine
ddI	didanosine
DLV	delavirdine
DOTS	directly observed therapy, short course
EFZ	efavirenz also known as EFV
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration (USA)
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
ICD	immune-complex-dissociated
IDU	injecting drug user
IDV	indinavir
LPV	lopinavir
MSF	Médecins Sans Frontières
MTCT	mother-to-child transmission
NAM	nucleoside analogue mutation
NFV	nelfinavir
NGO	nongovernmental organization
NIH	National Institutes of Health (USA)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NsRTI	nucleoside analogue reverse transcriptase inhibitor
NtRTI	nucleotide analogue reverse transcriptase inhibitor
NVP	nevirapine
OI	HIV-related opportunistic infection
PCP	Pneumocystis carinii pneumonia
PCR	polymerase chain reaction
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PPD	purified protein derivative skin test for TB
QA	quality assurance
r	low-dose ritonavir boost
RT	reverse transcriptase
RTV	ritonavir
STI	sexually transmitted infection
SQV	saquinavir
TAB	treatment advisory board
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLC	total lymphocyte count
UN	United Nations
UNAIDS	United Nations Joint Co-sponsored. Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session on HIV/AIDS
VCT	HIV voluntary counselling and testing
WHO	World Health Organization
ZDV	zidovudine

PREFACE

Less than a decade ago, someone living with HIV/AIDS had little hope.HIV infection brought a steady inexorable decline towards the complete destruction of the immune system and death. The introduction of ARVs in 1996 was a turning point for hundreds of thousands of people with access to sophisticated health care systems. Although they cannot cure HIV/AIDS, antiretrovirals (ARVs) have dramatically reduced mortality and morbidity, prolonged lives, and improved the quality of life of many people living with HIV/AIDS.

Today we are once again at a turning point - this time in favour of the developing world. Thanks to the work of hundreds of individuals and activists in NGOs, governments, UN agencies and the private sector, prices of ARVs have fallen and we are now in a position to consider scaling up access in resource limited settings.

Scaling up will not be possible in the absence of a clear public health approach that promotes the rational and safe use of these powerful and precious medicines. These technical guidelines, developed with the support of the US National Institutes of Health, present such an approach, promoting the use of standardized regimens and simplified monitoring. They recommend standards for the large-scale introduction of ARVs that prevent misuse. This is essential for good patient adherence and correct use by prescribers.

WHO estimates that in 2002, some 6 million people in developing countries are in need of life-sustaining ARV therapy now. Instead, only 230,000 have such access today, and half of these live in one country, Brazil. We believe that the countries of the developing world should be able to have 3 million people on ARVs by the end of 2005 – provided that the world follows through on the international concerted effort to expand access to HIV treatment and care. This ten-fold increase matters for many reasons. Three million people will be granted a new lease on life, wider access to treatment will stimulate prevention and there will be positive impacts on social and economic development as people living with HIV live longer and more productive lives.

These guidelines offer a chance of hope to those who despaired. They affirm the human rights and dignity of people living with HIV. They represent an opportunity to build upon the solidarity and energy of the global movement against HIV/AIDS by redressing the inequities between rich and poor in access to care. They will be updated on a regular basis as new information and evidence becomes available. As we look to the future, WHO will continue to work with its partners around the world to further increase access to care and support to all who need it.

Tomris Türmen
Executive Director
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Geneva
April 2002

SUMMARY

These guidelines are part of the World Health Organization's commitment to the global scale-up of antiretroviral therapy. Their development involved international consultative meetings throughout 2001, in which more than 200 clinicians, scientists, government representatives, representatives of civil society and people living with HIV/AIDS from more than 60 countries participated. The recommendations included in this document are largely based on a review of evidence and reflect the best current practices. Where the body of evidence was not conclusive, expert consensus was used as a basis for recommendations. We hope that this guidance will help Member countries as they work towards meeting the global target of having three million people on antiretroviral therapy by 2005.

A. When to start ARV therapy

WHO recommends that, for ARV treatment programmes in resource-limited settings, HIV-infected adolescents and adults should start ART when they have:

- WHO stage IV of HIV disease (clinical AIDS), regardless of the CD4 count;

- WHO stages I, II or III of HIV disease, with a CD4 count below 200/mm^3;

- WHO stages II or III of HIV disease with TLC below 1200/mm^3.

Wherever possible, countries are encouraged to use CD4 cell counts in their ARV treatment programmes and to consider the use of simple low-cost CD4 methodologies that are currently available in order to enable the wider use of such counts in their programmes. CD4 percentages may be used instead of total CD4 counts. A CD4 percentage below 15% corresponds to a total CD4 count of less than 200/mm^3. However, in cases where CD4 counts cannot be assessed the presence of a total lymphocyte count of 1200/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 count, in combination with clinical staging it is a useful

marker of prognosis and survival. An assessment of viral load, e.g. using plasma HIV-1 RNA levels, is not considered an essential preliminary to therapy.

In children, WHO recommends offering ARV combination therapy to HIV-positive infants under the age of 18 months if they have infection that has been virologically proven (using either HIV PCR or immune-complex-dissociated HIV p24 antigen detection or HIV culture) and WHO paediatric stage III HIV disease (i.e. clinical AIDS) or WHO paediatric stages I and II disease and a CD4 percentage below 20%. In settings where virological confirmation is not available, ARV combination therapy can be offered to HIV-positive infants who have WHO stage III HIV disease and a CD4 percentage below 20%. For children aged over 18 months who are HIV-antibody-positive, WHO recommends ART if they have WHO stage III HIV disease (i.e. clinical AIDS), regardless of the CD4 percentage. For those older children with WHO stage I or II HIV disease, ART is recommended if the CD4 percentage is below 15%.

B. Recommended first-line ARV regimens

Countries are encouraged to adopt a public health approach in order to facilitate the scale-up of ARV use in resource-limited settings. This means that antiretroviral treatment programmes should be developed and that ARV treatment should be standardized. In particular it is suggested that countries select a single first-line and a limited number of second-line regimens for large-scale use, while recognizing that persons who cannot tolerate or who fail the first-line and second-line regimens would be referred for individualized care by specialist physicians.

Matters that should be considered in connection with selecting ARV treatment regimens at both the programme level and at the level of the individual patient include potency, the side-effect profile, the potential for maintaining future treatment options, the anticipated adherence of the patient population to a regimen, coexistent conditions (e.g., coinfections, metabolic abnormalities), pregnancy or the risk thereof, the use of concomitant medications (i.e. potential drug interactions), the potential for primary acquisition of resistant viral strains, cost and access. Additional factors that may have to be considered in resource-limited settings include access to only a limited number of ARV drugs, a limited health service infrastructure, the need to deliver drugs to rural areas, a high incidence of tuberculosis and hepatitis B and/or C, and the presence of various HIV groups and subtypes.

Taking all of these considerations except the cost of drugs into account, the preferred first-line antiretroviral regimens in adults and adolescents are listed in Table 3. All regimens consist of a dual nucleoside component and a potent third drug to complement it. Zidovudine (ZDV)/lamivudine (3TC) is listed as the initial recommendation for the dual nucleoside component based on efficacy, toxicity, clinical experience and the availability of ZDV/3TC as a fixed-dose combination. Other dual nucleoside combinations can be substituted for ZDV/3TC, including stavudine (d4T)/3TC, d4T/didanosine (ddI) and ZDV/ddI, depending on country-specific preferences. However, ZDV and d4T should never be used together because of proven antagonism between these drugs.

It should be noted that dual nucleoside drug regimens alone are no longer recommended as they do not adequately suppress HIV replication and are likely to lead to the rapid emergence of resistance.

The advantages of the dual nucleoside plus non-nucleoside regimens are that the drugs are widely available at affordable cost and reasonable pill counts and that the regimens are potent. The main disadvantages are the development of drug resistance, the potential hepatotoxicity of nevirapine (NVP), and the need to have separate regimens for men and women because the potential teratogenic effects of efavirenz (EFZ) preclude the use of this drug use in pregnant women or women of childbearing age who are at risk of an unintended pregnancy. Countries with a significant prevalence of HIV-2 as well as group O HIV-1 viruses might consider reserving the use of the regimens containing non-nucleosides for patients with proven HIV-1 infection, because HIV-2 as well as group O HIV-1 viruses are naturally resistant to this class of drugs.

The ZDV/3TC/abacavir (ABC) regimen is the most user-friendly from the standpoint of both patients and programmes: only two pills a day are required and there are no significant drug interactions. Its main disadvantages are some uncertainty as to whether it works when the viral load is very high in patients with very advanced disease, uncertainty as to whether the drugs, particularly ABC, will become available at an affordable cost, and the potential for causing fatal hypersensitivity reactions that could escape detection in resource-poor settings. There are relatively limited data on the efficacy of other potential triple nucleoside reverse transcriptase inhibitor (NsRTI) combinations. This precludes WHO from recommending them at this time.

The advantage of the dual nucleoside plus protease inhibitor (PI) regimen is its proven high potency in reducing viral loads. The disadvantages are higher pill counts and significant interactions with other drugs, precluding or complicating their use during TB treatment with rifampicin, metabolic abnormalities, and the need for a functioning cold chain for ritonavir-boosted regimens.

C. Reasons for changing ART

ART may need to be changed because of either treatment failure or toxicity. Treatment failure can be evaluated clinically, immunologically by measurement of the CD4 count, and/or virologically by measuring viral loads. However, as the latter are not normally available in resource-limited settings it is recommended that programmes in such settings should primarily use clinical criteria and, where possible, CD4 counts, to define treatment failure.

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

If a change in regimen becomes necessary because of treatment failure, a new second-line regimen is required. If a change in regimen is indicated because of toxicity, either an entirely new second-line regimen can be prescribed or, if the toxicity is related to an identifiable drug, the latter can be replaced with another drug that does not have the same side-effects.

D. Choice of second-line ARV regimens

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

Table 4 lists the second-line regimens that could be considered for adolescents and adults in respect of each of the first-line regimens identified in Table 3. For ZDV/3TC a reasonable alternative dual

nucleoside component is d4T/ddI. In addition, ZDV/ddI can replace d4T/3TC and vice versa, although nucleoside analogue cross-resistance is an increasing concern.

When ZDV/3TC is used in the first-line regimen, nucleoside cross-resistance may compromise the potency of d4T/ddI in the second-line regimen, particularly in the presence of long-standing virological treatment failure. As the chances of cross-resistance are somewhat reduced when switching to ABC/ddI in comparison with switching to d4T/ddI, the former might also be considered as the nucleoside backbone for a second-line regimen if the first-line regimen does not include ABC. However, high-level ZDV/3TC resistance also confers diminished susceptibility to ABC.

Given the diminished potential of almost any second-line nucleoside component, one of the RTV-PI components [indinavir (IDV)/r, lopinavir (LPV)/r, saquinavir (SQV)/r] is preferred to nelfinavir (NFV) in second-line regimens because of their potency. NFV can be considered as an alternative for the PI component if an RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

E. Considerations for specific subgroups of patients

1. Women of childbearing potential or pregnant women

WHO recommends the use of ZDV, 3TC, NVP, NFV and SQV combined with low-dose ritonavir, as these have been the most widely used ARVs in pregnant women. EFZ is not recommended for use in women who could become pregnant because of its potential teratogenic effect on fetuses in the first trimester.

The choice of ART in women with the potential to become pregnant must take into account the possibility of the ARV drugs being received early in the first trimester, before recognition of pregnancy and during the primary period of fetal organ development. In order to reduce the likelihood of unintended pregnancy, effective and appropriate contraceptive methods should be available to women who are receiving ART. It is important to note that some antiretroviral drugs (the NNRTIs NVP and EFZ and all the RTV-boosted PIs) can lower blood concentrations of oral contraceptives and that additional or alternative contraception is necessary in order to avoid pregnancy in women receiving these drugs.

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

2. Children

The limited studies of HAART in children suggest that broadly similar improvements are seen in surrogate markers with many different ART regimens.

Most ARVs available for adults are also available for children. Specific formulations for children include dosages based on either body surface area or weight. First-line treatment options for children include ZDV/3TC plus either a non-nucleoside (NVP or EFZ) or ABC, but EFZ cannot be used in children under the age of 3 years because of a lack of appropriate dosing information. However, EFZ would be the non-nucleoside of choice in children on rifampicin in the event that ART needed to start before antituberculous therapy was completed. Second-line therapy for children in the event of first-line regimen failure would include a change in the nucleoside backbone (e.g. from ZDV + 3TC to d4T + ddI) plus a PI. The use of PIs other than LPV/r and NFV is problematic in children because of a lack of suitable paediatric drug formulations for IDV and SQV.

3. People with tuberculosis and HIV coinfection

WHO recommends that people with TB/HIV complete their TB therapy before beginning ARV treatment unless there is a high risk of HIV disease progression and death during the period of TB treatment (i.e. if the CD4 count is below 200/mm^3 or if disseminated TB is present). If a person needs TB and HIV treatment concurrently, first-line treatment options include ZDV/3TC or d4T/3TC plus either a non-nucleoside or ABC. If a non-nucleoside regimen is used, EFZ would be the preferred drug as its potential for aggravating the hepatotoxicity of TB treatment appears smaller than that of NVP. However, its dosage may need to be increased to 800 mg/day. Except for SQV/r, protease inhibitors are not recommended during TB treatment with rifampicin because of their interactions with this drug.

4. Injecting drug users

Injecting drug users who are eligible for ART should be ensured access to this life-saving therapy. Special considerations for this population include dealing prospectively with lifestyle instability, which challenges drug adherence, and accounting for the potential drug interactions of ARVs with agents such as methadone. The development is encouraged of programmes that integrate care related to drug dependence and HIV. In such settings, approaches such as directly observed therapy can be implemented. Once-daily ARV regimens are being explored in this arena and they lend themselves to such approaches.

5. Adherence to antiretroviral therapy

WHO recommends the development of innovative strategies for enhancing adherence to ART because of its lifelong nature.

Such strategies include minimizing pill counts and dosage frequencies by preferentially using combination pills on a once-daily or twice-daily basis. A number of fixed-dose combination products containing two or three ARV drugs, currently on the market, can be used twice a day. However, while a number of ARV drugs have been approved for once-daily administration, relatively few three-drug or four-drug once-daily regimens have been rigorously tested in clinical trials. Other approaches that might facilitate adherence include: enlisting the assistance of family or community members to support patients in taking their medications on a regular and timely basis; extensive counselling and education of patients; and directly observed therapy. Psychosocial issues that can contribute to low adherence to therapy should also be taken into consideration, especially for injecting drug users and other vulnerable populations.

6. Drug resistance surveillance

WHO recommends that each country planning to implement an ART programme should concurrently introduce an HIV drug resistance sentinel surveillance system. Such a system allows the detection of potential drug resistance at the population level and the modification of recommended treatment regimens accordingly. A Global HIV Drug Resistance Surveillance Network is being established by WHO in collaboration with partner organizations in order to assist Member States in this matter.

7. Clinical and laboratory monitoring of ARV use

WHO recommends that in resource-limited settings the basic clinical

assessment preceding the initiation of ART should include the documentation of past medical history, the identification of current and past HIV-related illnesses, the identification of coexisting medical conditions such as TB or pregnancy which may influence the choice of therapy, as well as current symptoms and physical signs.

In order to facilitate the scale-up of ARV use in resource-limited settings, WHO has prioritized currently available testing in the following categories:

- absolute minimum tests;
- basic recommended tests;
- desirable tests;
- optional tests.

Absolute minimum tests are a prerequisite for the introduction of ART in a national programme. Basic recommended tests are commonly used in the clinical setting and are needed to provide effective monitoring of most ARV regimens. Because of the urgency of providing potentially life-prolonging care to so many millions of people, WHO seeks to minimize the impediments to care. Consequently, the basic recommended laboratory tests are not considered to be absolutely essential for starting treatment, although they should be available where the necessary resources exist. Desirable tests can increase the effectiveness of the monitoring and evaluation of programme effectivenesss. Optional tests can be used in resource-rich settings.

The absolute minimum of laboratory tests required before initiating ART are an HIV antibody test and a determination of the haemoglobin level or the haematocrit. The rationale is that proof of HIV infection is needed before starting ARV therapy in the first instance, and screening for anaemia is essential before starting zidovudine-containing regimens.

Basic recommended testing should include a white blood cell count and differential (to permit assessment of neutropenic side-effects and the total lymphocyte count), the determination of serum alanine or aspartate aminotransferase in order to assess the possibility of hepatitis coinfection and to monitor for hepatotoxicity, the determination of

serum creatinine and/or blood urea nitrogen in order to assess baseline renal function, the determination of serum glucose, and pregnancy tests for women. These tests are not absolutely essential but are highly recommended in order to be able to provide monitoring for the safe use of the agents and to inform decisions about switching between regimens. CD4 cell counts are not listed at present as basic recommended tests. However, the introduction of simpler and less costly methods could lead to CD4 cell counts becoming more widely available. WHO recommends that this be considered a priority issue because CD4 cell counts are the best indicator of the immunological response to treatment.

Desirable tests include those for bilirubin, amylase and serum lipids and CD4 cell testing. These tests, while not absolutely essential, are felt to provide significant information that would be beneficial in the monitoring of ARV use in resource- limited settings. Viral load testing is currently considered optional because of resource constraints. Clinical monitoring is essential for the provision of safe and effective ARV therapy. Where laboratory monitoring is limited, close clinical monitoring becomes even more crucial.

WHO also has categorized laboratory tests according to the levels in the health service where they could be used. Simple rapid HIV diagnostic tests and sample referral for CD4 testing should be feasible at the primary care and district levels. Facilities at the district level should also be able to offer testing for pregnancy, haemoglobin, liver function, creatinine and glucose. In addition to the above- mentioned tests, facilities at the provincial level should be able to offer CD4 cell tests. Viral load testing and viral resistance assays should be made available at the central level if resources permit.

I. INTRODUCTION

Less than a decade ago, when the only available class of ARV drugs was unable to adequately inhibit HIV replication, the lives of people living with HIV/AIDS throughout the world followed an often immutable course: gradual destruction of the immune system, initiation of prophylaxis to prevent opportunistic infections, early retirement, wasting, periods of wellness and illness punctuating an inexorable decline towards complete immune depletion and, finally, death.

Since 1996 the way in which people in the richest countries think about HIV/AIDS has changed because of the advent of new classes of ARV drugs and their use in combination. These treatments are not a cure and they present new challenges of their own to people living with HIV/AIDS. Nevertheless, they have dramatically improved rates of mortality and morbidity, prolonged lives, improved the quality of life, revitalized communities and transformed perceptions of HIV/AIDS so that it is seen as a manageable chronic illness rather than as a plague.

Unfortunately, most of the 36 million people in the developing world currently living with HIV/AIDS do not share this vastly improved prognosis. WHO conservatively estimates that in 2002 some 6 million people in resource-limited settings are in *immediate* need of life-sustaining ARV therapy. Instead, only 230 000 have access to ARVs. Half of these people live in Brazil.

In the wake of the International AIDS Conference in Durban in 2000 and the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) in 2001, the resolve of the international community to address this appalling disparity between treated and untreated, between rich and poor, is stronger than ever. The world recognizes the pressing moral, social, political and economic need to expand access to antiretroviral therapy to many more millions of people living with HIV/AIDS as soon as practicable, and has begun to mobilize the ‘great global alliance’ requested by the UN Secretary-General in order to achieve the UNGASS goals.

These guidelines are part of WHO’s commitment to this alliance. Their development involved international consultative meetings throughout 2001 in which more than 200 clinicians, scientists, government representatives, representatives of civil society and

people living with HIV/AIDS from more than 60 countries participated. The recommendations included in this document are largely based on a review of evidence and reflect the best current practices. Where the body of evidence was not conclusive, expert consensus was used as a basis for recommendations. WHO recognizes that, in this rapidly evolving field, the recommendations will have to be regularly updated.

Although an important step, this document is not intended to be a 'magic bullet' for expanding access to ARV treatment. Drug access for the millions who need it can be improved not only by guidance on the rational selection and use of ARV drugs but also by improved affordability and sustainability of drug financing and by accessible, appropriate and competent health services. These other critical elements continue to be promoted by actors within and beyond the UN system through:

- the Accelerating Access Initiative, which had led to dramatic reductions in the cost of ARV drugs in 20 developing countries by January 2002;

- the mapping of sources and prices of HIV-related drugs by UNICEF, UNAIDS, MSF and WHO;

- the assessment by WHO and UNAIDS of the patent situation relating to HIV-related drugs;

- increased financial and human resources for efforts by WHO to strengthen the capacity of health systems in respect of HIV/AIDS, including the launching of an international network of training institutions for HIV care;

- the Global Fund to Fight AIDS, Tuberculosis and Malaria, launched by the UN Secretary-General in 2001, representing a significant new investment in combating these three major infectious conditions.

II. OBJECTIVES OF THE DOCUMENT

Currently, fewer than 5% of persons needing ARV drugs in resource-limited settings have access to these medicines. WHO believes that at least three million people needing care should be able to obtain them by 2005. This would represent an increase of more than tenfold.

These guidelines are intended to support and facilitate the proper management and scale-up of ART in the years to come by means of a public health approach, the key tenets of which are:

1) scaling up antiretroviral treatment programmes to meet the needs of people living with HIV/AIDS in resource-limited settings;

2) standardization and simplification of ARV regimens to support the efficient implementation of treatment programmes;

3) ensuring that ARV treatment programmes are based on the best scientific evidence, in order to avoid the use of substandard treatment protocols that compromise the outcome of treatment in individual clients and create the potential for the emergence of drug-resistant virus.

While it is hoped that this document will be useful to clinicians in resource-limited settings, it is intended primarily for use by treatment advisory boards, national AIDS programme managers and other senior policy-makers involved in the planning of national and international HIV care strategies in these settings. The guidelines serve as a framework for selecting the most potent and feasible antiretroviral regimens as part of expanded national responses. The framework aims to standardize and simplify ART, as has happened with 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 needs of health systems that often lack sophisticated manpower and monitoring facilities, without compromising the quality and outcomes of the treatments offered.

The topics addressed in these guidelines include ART, which ARV regimens to start, reasons for changing ART, and which regimens to continue if treatment needs to be changed. Also considered is the way in which treatment should be monitored, with particular reference to the side-effects of ART, and specific recommendations are made for certain subgroups of patients

III. BACKGROUND AND PURPOSE

The HIV epidemic began more than 20 years ago. WHO and UNAIDS estimate that more than 40 million persons were infected by the end of 2001 and that approximately 25 million people had died [1-4]. Over 90% of the infected persons live in the developing world where access to ARVs is the exception rather than the rule. WHO estimates that less than 5% of the people needing ARV treatment in developing countries have access to it. The dramatic reductions in morbidity and mortality that the introduction of potent ARV treatment brought about in the developed world have not occurred in most areas where the need is greatest [5-10]. In the past two years a dramatic sequence of events has provided the stimulus for redressing this injustice. They include the World AIDS Conference in Durban in 2000, which led to an acute awareness of the scope of the problem, the reduction in the price of antiretroviral agents, the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria, and a worldwide, multisectoral mobilization against AIDS, which found its clearest expression in the UNGASS Declaration of Commitment. The latter urged that HIV care and HIV prevention should be complementary, and committed governments to providing the highest attainable standard of care, including ARV treatment for people living with HIV/AIDS (Article 55, UNGASS Declaration, 2001). Antiretroviral treatment should be seen in the context of an overall essential care package for HIV-infected persons and as an integral complement to HIV prevention programmes. The provision of antiretroviral treatment can reinforce effective prevention campaigns, stimulate voluntary counselling and testing and help to destigmatize HIV infection. Furthermore, antiretroviral drugs have proved highly effective in preventing mother-to-child transmission (MTCT) of HIV and have the potential to decrease sexual transmission in the general population [11, 12].

Guidelines for ART have, in general, been developed for application in high-income and middle-income countries. All of these guidelines, including those developed by WHO for resource-constrained settings, have focused on individual case management [13-16]. The present document may be useful to clinicians practising in resource-limited settings but it is not a substitute for programme manuals. Such a manual will have to be developed by each ARV treatment programme once it has decided which first-line regimen and which second-line regimen or regimens to use and how it will

monitor treatment among its patients. These guidelines are intended to facilitate the dramatic scale-up that is needed in countries with limited infrastructures and significant resource limitations in order to provide care to millions of infected people.

Consequently, the purpose of this document is to provide guidance for the design of ARV treatment programmes by national AIDS control programmes in resource-limited settings. In particular it provides options for the selection of treatments that might be preferentially included in ARV treatment programmes taking into account the needs of specific subpopulations of people living with HIV/AIDS. It also offers guidance for monitoring ART.

The document is targeted primarily at health care planners and secondarily at the clinicians who assist them with the design of their programmes. A key element of the public health approach is to provide potent and effective ARV therapies that maximize the benefits for individual participants in programmes and preserve the treatment prospects of future participants, taking account of the special circumstances in the developing world. These include factors such as the high prevalence of TB, viral hepatitis and other comorbidities, as well as limitations in financing, drug management systems, health care personnel, facilities and monitoring capacity. This can only be achieved if the selected treatments suppress viral replication in a high proportion of individuals. Only maximal suppression of viral replication can prevent the emergence of resistant strains.

This paradigm uses a public health approach in order to facilitate scale-up. These new guidelines, providing choices for first-line and second-line ARV regimens, are for use by treatment advisory boards (TABs) of countries and other senior policy-makers involved in planning national and international HIV care strategies in response to the HIV/AIDS pandemic. TABs of Member States are encouraged to choose a specific first-line and one or two second-line ARV combination regimens for widespread use in their health care systems. This approach enables health care workers to prescribe and monitor ARVs with minimal training and limited access to laboratory support, thereby decreasing the training needs and making procurement easier.

IV. APPROACH TO ANTIRETROVIRAL THERAPY

A rational approach to ARV therapy derives from the evolving understanding of disease pathogenesis. The only regimens potent enough to drastically reduce viral replication, prevent the emergence of resistance and, ultimately, prevent treatment failure for a significant amount of time, have involved combinations of at least three ARVs [17-25]. Such regimens have been associated with immunological restoration, a slowing of disease progression, durable therapeutic responses, improvements in the quality of life, and prevention of the emergence of drug resistance [8, 26-43]. The reductions in morbidity and mortality resulting from the introduction of potent ART have been confirmed in all settings in which it has been used, including developing countries, e.g. Brazil, Senegal, Thailand, and Uganda [9, 44-47].

Recommendations for HIV-infected adult males and non-pregnant women form the core of this document. The issues unique to pregnant women, children, patients with comorbid infections and injecting drug users are addressed in separate chapters in order to make the document comprehensively useful and to reinforce the principle that access to care is a right of all HIV-infected persons. Post-exposure prophylaxis for accidental exposure to HIV and the prevention of MTCT of HIV are important uses of ARV drugs but are not within the purview of this document. WHO addresses these uses of ARVs separately.

V. WHEN TO START ANTIRETROVIRAL THERAPY IN ADULTS AND ADOLESCENTS

WHO recommends that, in resource-poor settings, persons with symptomatic disease (AIDS, WHO adult stage IV and advanced stage III disease) should receive ARV treatment irrespective of the CD4 cell or total lymphocyte count. Therapy is also recommended for people with earlier symptomatic (WHO adult stages II and III) and asymptomatic (WHO adult stage I) disease when the CD4 cell count nears or falls below 200/mm^3 or when the CD4 percentage is below 15% (Table 1). When CD4 cell monitoring is unavailable, treatment is recommended for symptomatic persons (WHO adult stages II and III) with TLCs below 1200/mm^3 (Table 1, Annex 1). However, when only TLCs are available, asymptomatic persons needing therapy cannot be accurately identified and only become eligible for treatment when their HIV disease progresses and symptoms are apparent. Wherever possible, countries are encouraged to utilize the currently available simple low-cost CD4 methodologies.

The recommendation to start treatment in asymptomatic patients only when the CD4 count drops below 200/mm^3 takes account of the following major unanswered question relating to ART. When should treatment be initiated in the setting of established infection among asymptomatic HIV-positive persons? While beginning therapy before the CD4 cell count falls below 200/mm^3 clearly provides clinical benefits, the actual point above 200/mm^3 at which to start therapy has not been definitively determined [48-52].

It is recognized that the availability of affordable and accurate CD4 cell testing is severely constrained in many of the countries where the majority of people in urgent need of treatment live. However, a TLC below 1200/mm^3 has proved useful in the presence of HIV-related symptoms. While the TLC correlates relatively poorly with the CD4 count, in combination with clinical staging it is a useful marker of prognosis and survival [53-59] (Table 1). In asymptomatic HIV-infected individuals, however, the TLC is less useful. Treatment cannot, therefore, be recommended in such patients on the basis of the TLC alone. This highlights the urgent need for the development and implementation of techniques for CD4 cell determination which are inexpensive and applicable in developing countries.

Table 1. Recommendations for initiating antiretroviral therapy in adults and adolescents with documented HIV infection

If CD4 testing is available:
• WHO stage IV irrespective of CD4 cell count[a]
• WHO stage I, II or III[a] with CD4 cell counts less than 200/mm^3 [b]
If CD4 testing is not available:
• WHO stage IV irrespective of TLC
• WHO stage II or III[c] with TLC less than 1200/mm^3 [c]

[a]Treatment is also recommended for patients with advanced WHO stage III disease, including recurrent or persistent oral thrush and recurrent invasive bacterial infections, irrespective of the CD4 cell count or the total lymphocyte count.

[b]The precise CD4 level above 200/mm^3 at which to start ARV treatment has not been established but the presence of symptoms and the rate of CD4 cell decline (if measurement is available) should be factored into decision-making. A CD4 level of 200/mm^3 corresponds to a CD4 percentage of approximately 15%.

[c]A total lymphocyte count below 1200/mm^3 can be substituted for the CD4 count when the latter is unavailable and HIV-related symptoms exist. It is less 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.

VI. RECOMMENDED FIRST-LINE REGIMENS FOR ADULTS AND ADOLESCENTS

WHO recommends that ARV treatment programmes in resource-constrained settings choose one potent first-line ART regimen with which to start treatment in the majority of patients. Clinical trials of different triple-drug regimens have generally revealed comparable antiviral potencies [32, 36, 39, 42, 63-65]. The choice among these regimens therefore generally relies on other considerations, including side-effect profiles, potential drug interactions, comorbidities (e.g. tuberculosis, hepatitis), the maintenance of alternative options in the setting of treatment failure, and drug availability and cost.

Of the 16 approved ARV agents for the treatment of HIV-1 infection in the USA, six are NsRTIs, one is an NtRTI, three are NNRTIs and six are PIs. Thirteen of these agents have been incorporated into the present guidelines (Table 2).

Table 2. Approved antiretroviral agents included in WHO's ARV guidelines[a]

Nucleoside reverse transcriptase inhibitors (NsRTIs)	**Nucleotide reverse transcriptase inhibitor (NtRTI)**	**Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**	**Protease inhibitors (PIs)**
zidovudine(ZDV, AZT)[b]	tenofovir disoproxil fumarate (TDF)	nevirapine (NVP)[b]	saquinavir (SQV)[b]
didanosine (ddI)[b]		efavirenz (EFZ)[b]	ritonavir (RTV) (as pharmacoenhancer)[b]
stavudine (d4T)[b]			indinavir (IDV)[b]
lamivudine (3TC)[b]			nelfinavir (NFV)[b]
abacavir (ABC)[b]			lopinavir/ritonavir (LPV/r)[b]

[a]Approved and generally available in industrialized countries as of January 2002.

[b]Approved for inclusion in WHO's Essential Drug List as of April 2002.

The recommended regimens (Table 3) each contain a dual nucleoside component (backbone) to be combined with a PI, an NNRTI or the potent NsRTI, abacavir (ABC). In this context the following potential dual NsRTI components have to be considered: zidovudine(ZDV)/lamivudine(3TC), stavudine(d4T)/3TC, d4T/didanosine (ddI), ZDV/ddI, ZDV/zalcitabine (ddC), and ddI/3TC. Of these, the first two have emerged as leading candidates for use in initial regimens because of their efficacy, toxicity profiles and years of clinical experience [30, 66, 67]. d4T/ddI remains an important dual nucleoside component of potent regimens but cautions have been raised about its potential to cause lactic acidosis, particularly in pregnant women, hepatotoxicity and neurotoxicity (both peripheral neuropathy and a condition resembling the Guillain-Barre syndrome)[68]. Among the NsRTIs, d4T has been most strongly linked to the development of lipoatrophy in some studies [69 -72]. Substantial clinical endpoint data support the use of ZDV/ddI [73, 74]. ddI can be administered once daily, and the recently introduced enteric coated formulation of ddI substantially improves tolerance of this drug. ddI/3TC appears to have comparable antiviral potency to the other dual NsRTI combinations listed but the data sets supporting its use are more limited. ddC has not been recommended because of the requirement for dosing three times daily and the incidence of peripheral neuropathy. Although direct comparative data are limited, these five dual nucleoside components appear to possess comparable inherent antiviral activity in treatment-naïve persons [66, 67, 75, 76]. On the grounds of efficacy, toxicity, clinical experience and fixed-dose combination availability, ZDV/3TC is recommended as the initial dual NsRTI component of choice. However, country-specific decision-making is encouraged (Table 3).

It should be noted that ABC can also be used as part of a dual NsRTI backbone in initial regimens but for the purposes of these guidelines its recommended use is restricted to the cornerstone of triple NsRTI regimens. Certain dual NsRTI components should never be used because of antiviral antagonism (e.g. ZDV and d4T)[77].

Tenofovir disoproxil fumarate (TDF), the latest addition to the approved antiretroviral armamentarium, is an NtRTI, requiring only intracellular diphosphorylation in order to be active against HIV reverse transcriptase. Operationally, it can be viewed as expanding the NsRTI options. It is considered later in this text because the bulk of clinical trial data have been developed in treatment-experienced populations. Given its tolerance and once-daily dosing, it has substantial potential as a component of once-daily regimens in treatment-naïve persons as well.

Dual NsRTI therapy alone is not recommended as initial therapy because the regimen potencies are suboptimal and the emergence of drug resistance is predictable. However, it is recognized that many HIV-infected individuals in the developing world are being treated with dual NsRTI combinations because potent three-drug and four-drug combinations are not affordable. As dual NsRTI therapy is considered suboptimal in these and other published guidelines, persons currently doing well on dual NsRTI regimens should be considered for switching to one of the potent regimens outlined in this document. If this is not deemed feasible or advisable because of country-specific resource constraints or individual physician/patient considerations, treatment should be continued for those persons who are deemed to be receiving continued benefit. This, however, is not an endorsement of the continued initial use of these regimens and every effort should be made to provide standard-of-care regimens for all patients in whom therapy is initiated.

In order to establish a potent ARV regimen a third drug must be added to the dual nucleoside backbone. The three combinations to consider involve the addition of one of the following: (1) an NNRTI; (2) abacavir; (3) a PI (+/- low-dose ritonavir for pharmacoenhancement). These combinations are PI-sparing, dual-class (i.e. PI- and NNRTI-sparing) and NNRTI-sparing respectively. This is important with respect to the maintenance of alternative treatment options following therapeutic failure. Although two other possible potent initial regimens exist, PI plus NNRTI plus NsRTI(s) or PI plus NNRTI, these are not considered here because they have been less well studied as initial regimens and are consequently not among the first-line options used for initial therapy in the developed world.

Suggestions of differences within and between these three basic regimens have begun to emerge: lopinavir/ritonavir (LPV/r) was associated with virological outcomes superior to those of nelfinavir (NFV) in one trial[78]. It should also be noted that there are only limited data on the use of ABC-containing triple NsRTI regimens in patients with advanced disease[39]. Although important, these clinical trial results are just one factor to be considered when deciding about which PI to employ or whether to use ABC in initial regimens. In general, therefore, the choice should rely on other considerations, including the side-effect profile, potential drug interactions, the maintenance of alternative options in the setting of treatment failure, and drug availability and cost.

Table 3. Recommended first-line antiretroviral regimens in adults and adolescents with documented HIV infection

Regimen[a]	**Pregnancy considerations**	**Major toxicities**
ZDV/3TC/EFZ or ZDV/3TC/NVP	Substitute NVP for EFZ in pregnant women or women for whom effective contraception cannot be assured	ZDV-related anaemia EFZ-associated CNS symptoms Possible teratogenicity of EFZ NVP-associated hepatotoxicity and severe rash NsRTI-related metabolic side-effects
ZDV/3TC/ABC[a]	ABC safety data limited	ZDV-related anaemia ABC hypersensitivity NsRTI-related metabolic side-effects
ZDV/3TC/RTV-PI[b] or ZDV/3TC/NFV	LPV/r safety data limited NFV: most supportive safety data	ZDV-related anaemia NFV-associated diarrhoea IDV-related nephrolithiasis PI- and NsRTI-related metabolic side-effects

[a]ZDV/3TC is listed as initial recommendation for dual NsRTI component based on efficacy, toxicity, clinical experience and availability of fixed-dose formulation. Other dual NsRTI components can be substituted, including d4T/3TC, d4T/ddI and ZDV/ddI, depending on country-specific preferences (see text). ZDV and d4T should never be used together because of proven antagonism. Fixed-dose formulations are preferred whenever possible as they promote enhanced drug adherence.

[b] RTV-PI includes IDV/r, LPV/r or SQV/r.

When available, fixed-dose combinations are advantageous with respect to the simplification of regimens and consequent improved adherence. The major pharmaceutical manufacturers currently produce three fixed-dose combinations included in these guidelines: ZDV/3TC, ZDV/3TC/ABC and LPV/r. Fixed-dose formulations have also been produced by generic manufacturers (e.g. d4T/3TC/NVP and ZDV/3TC/NVP), which may facilitate simplified regimens, decrease cost and promote adherence if they can be legally used and their quality and bioequivalence have been demonstrated.

All of the initial regimens discussed are applicable for drug-susceptible HIV-1 infection with the main subtypes. For group O HIV-1 subtype or HIV-2 infections, only the triple NsRTI and PI-based regimens should be used because of the inherent resistance of these viruses to the NNRTI class of compounds.

Drug dosages for adults are listed in Annex 7. Relevant drug toxicities and major drug interactions for the agents recommended are listed in Table 10 and Annexes 8 and 11. (See also Chapter XV.)

A. NNRTI-based regimens

NNRTIs are very potent anti-HIV-1 agents in general but are inactive against the group O HIV-1 subtype and HIV-2. There are three approved NNRTIs, but because of the pill burden and the thrice-daily dosing associated with delavirdine (DLV), the two drugs recommended are efavirenz (EFZ) and nevirapine (NVP). Each should be administered in combination with two NsRTIs (Table 3, Annexes 3 and 6). Clinical trial and cohort data suggest that triple-drug combinations involving either drug are at least comparable to PI-based regimens. Although experts at WHO meetings considered that the data for EFZ were possibly the more convincing [36, 42, 62], no definitive, comparative, randomized clinical trial data are yet available which allow differentiation between EFZ and NVP on the basis of potency. At present, therefore, the choice should be based on predicted tolerance and adherence, toxicity profiles, the presence of coexistent conditions such as pregnancy (or the potential to become pregnant), active tuberculosis or other significant coinfections, and drug availability. EFZ is now available as a single 600-mg tablet, and this further enhances the attractiveness of the drug. However, because *in utero* exposure to EFZ in primates has been shown to cause central nervous system and craniofacial abnormalities, the drug is contraindicated in women on ART who are pregnant or desire to become pregnant. For this reason, NVP should be considered the NNRTI of choice in women

of childbearing age unless effective contraception is used. The potential side-effects of NVP, including rash and, particularly, hepatotoxicity, should be considered. EFZ may diminish the effectiveness of oral contraceptives. If this drug is used, therefore, alternative contraceptive methods must also be employed.

B. Triple NRTI-based regimens

For the purpose of these guidelines, triple NsRTI-based regimens are considered to be those containing ABC because of the potency of this agent (Table 3, Annexes 4 and 6)[39, 79]. The bulk of the data for ABC-based triple NsRTI regimens have been developed in relation to the use of this agent combined with ZDV and 3TC but, given the comparable potency among the dual NsRTI components listed above, some flexibility in choice can be assumed. However, the availability of a fixed-dose combination containing ZDV, 3TC and ABC permits the delivery of a potent triple-drug combination with one pill administered twice daily. A low pill burden and a predicted high level of adherence are therefore major advantages of this approach. In addition, the lack of interaction with rifampicin and stability at room temperature are favourable characteristics. However, this regimen is of uncertain efficacy in patients with advanced disease, there is a risk of ABC hypersensitivity that may affect up to 5% of patients starting on the medication, and there are only limited data on the use of ABC in pregnancy. The risk of ABC hypersensitivity in regions with a high incidence of febrile illnesses such as malaria and tuberculosis could hinder accurate diagnosis of this potentially fatal side-effect.

C. Regimens based on protease inhibitors

Although there are six approved PIs, only four are recommended as first-line agents for reasons of tolerance, clinical trial experience and expert consensus on their applicability in resource-limited settings. These four agents are NFV, indinavir (IDV) combined with low-dose ritonavir (RTV), LPV/r, and saquinavir (SQV) combined with low-dose RTV (Table 3) [80, 81]. Amprenavir (APV) is not recommended for initial therapy because of the pill size and burden even when boosted with low-dose RTV; it is best used in the salvage setting pending the availability of the APV prodrug currently undergoing development. RTV in full dose as a single agent poses substantial tolerability problems that limit its utility; it is consequently best reserved for use in low doses as a pharmacoenhancer. A summary of the characteristics of the PI-based regimens is given in Annexes 5 and 6. Each of these PIs, in

combination with two NsRTIs, offers sufficient potency to be recommended in this context, but each has drawbacks. NFV is widely prescribed, does not require refrigeration, may provide more alternative options if resistance is detected early and the virus mutates along the D30N pathway, and is safe in pregnancy [37, 82-84]. However, the pill burden is moderate, diarrhoea is a common side-effect and the drug cannot be combined with rifampicin. IDV offers the advantage of potency and a substantial data set of experience, including clinical endpoint trials, to support its use [29-32, 41, 82, 85]. When the drug is combined with low-dose RTV for pharmacoenhancement it no longer needs to be taken on an empty stomach and IDV/RTV can be given twice daily. The pill burden remains higher than optimally desired, however, and applicability in tropical climates is a concern because a high daily fluid intake is required in an attempt to avoid nephrolithiasis and because it is necessary to refrigerate RTV for longer-term stability. Moreover, both IDV and RTV are incompatible with rifampicin. LPV/r, the most recently approved PI, offers the advantages of potency, coformulation that improves its pharmacokinetics, and relatively good tolerance. On the negative side, experience with LPV/r in pregnancy is limited, and the drug is incompatible with rifampicin. SQV, in combination with low-dose RTV, is another PI option. This combination has been more recently studied and has the advantage of being well tolerated and administered as a twice-daily or possibly a once-daily regimen. Furthermore, it has been reported as compatibile with rifampicin (see Chapter XII). The use of RTV permits either the soft-gel or the hard-gel formulation of SQV to be used; it appears that the latter is associated with a reduced incidence of gastrointestinal side-effects when used in this combination. The hard-gel capsule of SQV should not be administered without RTV pharmacoenhancement because of its low bioavailability when administered alone. The disadvantage of SQV/RTV is the relatively limited data set that currently exists. The need for refrigeration of current RTV formulations in order to achieve stability beyond 30 days is a problem for severely resource-constrained areas. However, where refrigeration is not possible in an individual's or family's home, clinic dispensing facilities should be able to store and dispense the agent to their patients on a regular basis or should develop this capacity.

The metabolic toxicities associated with ART in general and PIs in particular are a major concern and the subject of intense investigation [86, 87]. Descriptions of these and other toxicities associated with PIs are detailed in Table 10 and Annex 11 (see Chapter XV).

VII. WHEN TO CHANGE THERAPY IN ADULTS AND ADOLESCENTS

The reasons for altering an initial antiretroviral regimen include intolerance leading to poor adherence, drug toxicity, the occurrence of active tuberculosis or pregnancy, and treatment failure.

A. Changing because of failure

When considering a complete regimen switch for treatment failure, the first point for discussion is the definition of failure. Treatment failure can be defined as clinical, immunological and/or virological. Clinical failure is clinical disease progression with the development of an opportunistic infection or malignancy when the drugs have been given sufficient time to induce a protective degree of immune restoration. This needs to be differentiated from an immune reconstitution syndrome, which can be seen within the first several weeks after the institution of therapy if a subclinical infection is present at baseline [88]. Although the management of immune reconstitution syndromes can be difficult, changing the antiretroviral regimen in this circumstance is not indicated. Immunological failure can be defined as a fall of over 30% in CD4 counts from the peak value or a return to or below the pre-therapy baseline [16]. There is no accepted definition of immunological failure which can be used if CD4 counts are not available. Virological failure has no uniformly accepted definition but repeated, continued detectable viraemia is indicative of incomplete viral suppression. As measuring viral load is not an option in the majority of resource-constrained settings, and is not recommended for the routine monitoring of treatment in the present guidelines, the reader is referred to other guidelines [16] on the use of viral load monitoring of ARV treatment. However, it is to be hoped that this situation will change as less expensive approaches to viral load quantitation are developed.

B. Changing because of toxicity

In the setting of a good therapeutic response, the development of a clearly definable toxicity permits single drug substitutions without compromising the overall regimen. For example, d4T can be substituted for ZDV in the event of ZDV-related symptoms or anaemia, and NVP can be substituted for EFZ if EFZ-related symptoms affecting the central nervous system are unremitting. In

respect of other toxicities for which a specific causal agent cannot be identified, and/or of low-grade but intolerable side-effects that frequently compromise adherence, a complete regimen switch may be the most adequate and broadly implementable approach. The choice of approach partly depends on the formulary that is available in the country concerned. If an interruption in therapy is indicated in order to deal with toxicity the entire regimen should be temporarily stopped so as to prevent the emergence of drug resistance (see Chapter XV, Table 10 and Annex 11).

VIII. RECOMMENDED SECOND-LINE REGIMENS IN ADULTS AND ADOLESCENTS

WHO recommends that patients experiencing treatment failure should switch from a first- line to a completely different second-line combination regimen. A number of options for second-line regimens are provided wherever feasible (Table 4).

Table 4. Recommended second-line regimens in adults and adolescents

First-line regimens	Second-line regimens for treatment failure	Alternative second-line regimens for treatment failure
ZDV/3TC/EFZ or ZDV/3TC/NVP	d4T/ddI/RTV-PI[a,b,c]	RTV-PI[a]/ABC/ddI[c,d] NFV/ABC/ddI[c,d] or d4T/ddI[b,c]/NFV
ZDV/3TC/ABC	d4T/ddI[b,c]/EFZ or d4T/ddI/NVP	d4T/ddI[b,c]/RTV-PI[a]
ZDV/3TC/RTV-PI or ZDV/3TC/NFV	d4T/ddI[b,c]/EFZ or d4T/ddI/NVP	ABC/ddI[c,d] /EFZ or ABC/ddI/NVP

[a]RTV-enhanced PI = IDV/r, LPV/r, SQV/r. An RTV-enhanced PI regimen is preferred because of the potency of these regimens. NFV can be considered as an alternative for the PI component of second-line therapy if RTV-enhanced PI is not available or if there is a clinical contraindication to its use.

[b]Nucleoside cross-resistance may compromise the potency of d4T/ddI at the time of switching for treatment failure as it is assumed that virological failure will have been prolonged at that point and several nucleoside analogue mutations (NAMs) are likely to be present. However, choices are limited in the setting of treatment failure. See also footnote [c].

[c]Tenofovir is a once-daily nucleotide NtRTI with activity against some nucleoside-resistant strains. If available, TDF can either be added to d4T/ddI or ABC/ddI or substituted for either d4T or ABC in these combinations. Its currently restricted availability in resource-limited settings is recognized.

[d]High-level ZDV/3TC coresistance confers diminished susceptibility to ABC. If d4T/3TC is used as the first-line dual nucleoside backbone, AZT/ddI can be used as the second-line nucleoside component and vice versa.

If viral load and resistance monitoring are not used to define treatment failure, virological failure will probably have been present for an extended period when treatment failure is detected on clinical or immunological grounds. Consequently, viral replication will have led to the evolution of more drug resistance mutations than would have been the case if treatment failure had been detected earlier. Moreover, in the absence of testing for drug resistance, assumptions have to be made about which drugs have been compromised and which will probably remain useful. It is well accepted, for example, that failure on regimens which contain a PI and 3TC are associated with 3TC failure and the maintenance of PI susceptibility when the failure is detected early[89, 90]. Information from clinical trials can be used to predict drug resistance failure patterns (Annexes 3-5). The inferences made, however, based on the early selection of virological events, must be used cautiously if more prolonged treatment failure is being dealt with, as is very likely to be the case in resource-limited settings.

Knowledge of viral evolutionary pathways and of the potential for intra-class cross- resistance has been incorporated into the recommendations presented in Table 4. However, the limitations on drugs for effective salvage therapy and the lack of capabilities for monitoring viral load and drug resistance mean that certain degrees of cross-resistance may have to be accepted. In this regard, perhaps the most difficult question surrounding the empirical switch of a first-line regimen to a second-line regimen concerns the approach to the NsRTI component, which is related to the increasing recognition of the degree of cross-resistance that exists across this class of agents. Even where this cross-resistance may be subtle or incomplete, an insufficiently potent dual NsRTI component may compromise the core component of the newly introduced drugs (e.g. the PI or NNRTI).

In the case of PI and NNRTI regimens a switch of drug class is indicated from one to the other. The almost complete cross-resistance between EFZ and NVP means that a switch between these two agents in the setting of treatment failure is not advisable. If the original first-line regimen contains an NNRTI, ritonavir-boosted PIs are preferred to NFV alone because of their higher potency.

Cross-resistance among PIs is also common. A possible exception to this exists when NFV is the first PI utilized, because the signature mutation, D30N, seen with NFV failure, does not confer resistance to the other PIs. In the absence of resistance testing, however, the

presence of this mutation alone cannot be predicted with certainty because another pathway, characterized by the L90M mutation, may alternatively occur and lead to PI cross-resistance[84, 91]. In the event of treatment failure on a PI-based regimen, therefore, it is recommended that the PI be switched to an NNRTI. It is worth reiterating, however, that potential cross-resistance among NsRTIs may compromise the overall potency of this regimen, even when the dual NsRTI component is changed, and predispose to virological failure. However, in the absence of a capability for monitoring viral load and drug resistance, this empirical change in the setting of treatment failure is felt to be the most pragmatic approach. TDF, if it could be made available, could be useful in this setting (Table 4, footnote [c]).

In the case of ABC-based triple NsRTI regimens, two major drug classes have been spared, thus permitting a truly potent alternative regimen to be constructed. This would combine a PI with an NNRTI. It is reasonable but not mandatory to support the regimen with continued NsRTI therapy because some residual antiretroviral activity can be provided by this class of agents. ABC might still be useful if only the M184V mutation or a limited number of NsRTI-associated mutations have developed. TDF might prove useful as a supplement to a PI/NNRTI alternative regimen, given its activity against some NsRTI-resistant viruses[92-96]. Another alternative is to use an RTV-enhanced PI with two NsRTIs. An RTV-enhanced PI has a higher genetic barrier to resistance than an NNRTI and may provide some additional regimen potency in the setting of NsRTI class cross-resistance.

IX. DRUG RESISTANCE

Although resource limitations make it clear that testing for HIV drug resistance cannot be part of clinical management in low-income countries, the principles underlying the evolution of drug resistance are important in supporting the rationale for the delivery of potent regimens. Furthermore, it is important to monitor the prevalence and incidence of drug resistance on a population basis as ART is scaled up worldwide. In parallel with the promulgation of these guidelines and the facilitation of drug access for the developing world, WHO, in collaboration with the International AIDS Society, is instituting a Global HIV Drug Resistance Surveillance Network. The goals of this programme are to: (1) establish a network of institutions, laboratories and investigators in order to monitor the epidemiology of drug resistance prospectively on a global basis; (2) make this information available through a web site and published reports; (3) provide a resource for public health officials, clinicians and researchers in order to assist them with the development of regional and country-specific antiretroviral guidelines and strategies aimed at preventing the further spread of drug resistance.

The following factors could facilitate the evolution and spread of drug resistance.

- Reliance on clinical and CD4 cell monitoring in the absence of viral load monitoring to detect treatment failure, which would allow viral replication to persist longer before a regimen switch than in situations where switching is based on some level of detectable viraemia [36, 40, 41, 97].

- The intrinsic resistance of group O HIV-1 subtype and HIV-2 to NNRTIs and the possibility that other subtypes may follow unique or predominant resistance pathways under drug-selective pressure [45, 46, 98-103].

- Failure to continue to emphasize safe sexual practices and other harm reduction interventions for the prevention of virus transmission.

- Potential interruptions in drug supply. If this occurs, unintended treatment interruptions can ensue and predispose to the emergence of drug resistance. If the supply of one component

of a multidrug regimen is interrupted, the entire regimen should be temporarily stopped until all the drugs can be administered simultaneously.

An important but unanswered question concerns the influence of MTCT prevention programmes utilizing regimens of limited potency (e.g. NVP or ZDV/3TC) on the subsequent treatment of the mother and the infected infant. This issue is addressed in Chapters X and XI.

It is well established that the introduction of any antimicrobial therapy for an infectious disease is associated with the induction and spread of drug resistance as an inevitable consequence. Although an obvious concern, this is not a reason to delay the introduction of large-scale ART programmes. An appropriate response should involve the education of providers and patients, strict attention to drug adherence, monitoring the population for drug resistance, and the introduction of strategies aimed at limiting it. On a more optimistic note, it is possible that the risk of the spread of resistant virus strains in the population may be balanced by the potential for reducing HIV transmission through the introduction of ART. Another question is whether drug-resistant viruses with reduced fitness are less transmissible than others[104]. These questions should be dealt with as part of an international research effort that should proceed in parallel with the introduction of service programmes.

A regularly updated list of HIV drug resistance mutations is available on the web site of the International AIDS Society – USA (www.iasusa.org).

X. ANTIRETROVIRAL THERAPY IN WOMEN, WITH SPECIFIC REFERENCE TO PREGNANCY

ART recommendations for HIV-infected pregnant women are based on the principle that therapies of known benefit to women should not be withheld during pregnancy unless the risk of adverse effects in the mother, fetus or infant outweighs the expected benefit to the woman concerned [105]. Pregnancy, or the desire to become pregnant, should not preclude the use of optimal antiretroviral therapy. However, considerations related to pregnancy may affect decisions regarding the choice of an antiretroviral regimen. Additionally, the potential impact of such therapy on the fetus and infant must be considered when treating women of childbearing age unless they use effective contraceptives. For pregnant women who do not yet need ART for their own disease, the use of antiretroviral drugs to reduce the risk of MTCT of HIV is recommended [106-110]. However, a discussion of ARV therapy for this indication falls outside the scope of the present guidelines. The reader is referred to the recent WHO guidelines on MTCT for further information.

A. Choice of antiretroviral drugs in non-pregnant women of childbearing age

The choice of ART in women with the potential to become pregnant must take into account the possibility of the drugs being received early in the first trimester. By the time that pregnancy is recognized by most women the fetus will have had drug exposure during the period of highest risk for the induction of birth defects by a teratogenic drug. Effective contraceptive methods should be available to women who are receiving ART, so as to reduce the likelihood of unintended pregnancy. Drugs with potential reproductive toxicity to the developing fetus, such as EFZ, should be avoided in women who may become pregnant. The NNRTIs and PIs can lower estrogen and/or norethindrone blood concentrations in women receiving oral contraceptives (Annex 8). Women using oral contraceptives who are receiving these classes of antiretroviral agents must therefore use additional or alternative contraception. There are insufficient data on drug interactions with injectable hormones for it to be possible to make recommendations on the need for additional contraception. Theoretically, since hormone levels are much higher with injectable than with oral

contraceptives, interactions between the former and antiretroviral drugs may be less significant.

There are insufficient data to definitively determine the risk of birth defects in humans with exposure to antiretroviral drugs administered during the first 10 to 12 weeks of gestation. In developed countries the experience gained with women who receive ZDV and/or 3TC during the first trimester makes it possible to conclude that the rate of birth defects in their infants does not appear to be higher than that in the general population of the USA (approximately 2-3%) [111]. However, there are minimal data available for other drugs and for the use of drugs in combination regimens, and studies in animals provide the basis for most data on safety in pregnancy (Table 5).

Certain antiretroviral drugs are of more concern than others. Significant birth defects of the central nervous system (anencephaly, anophthalmia, cleft palate) were observed in 3 of 20 infants born to monkeys that received EFZ during early pregnancy at doses resulting in plasma concentrations comparable to those seen with human therapeutic exposure [112, 113]. Additionally, there has been a case report of myelomeningocele in a human infant born to a woman who was receiving EFZ at the time of conception and during the first trimester [114, 115]. Consequently, EFZ should be avoided in women who desire to become pregnant and in women of childbearing potential overall unless adequate contraception is available and is being used and unless the women are counselled about the potential risk to the fetus should pregnancy occur.

B. Choice of antiretroviral drugs in pregnancy

Physiological changes that occur during pregnancy may affect the absorption, distribution, metabolism and elimination of drugs. This could affect the dose of drug required to reach therapeutic levels in a woman and the effectiveness of the drug therapy. These pharmacological changes could also potentially alter the susceptibility of the pregnant woman to drug toxicity. Additionally, pregnancy itself could alter susceptibility to certain toxicities. Considerations about choice of ARVs in pregnancy must also take into account the potential effect of the drugs on the fetus and infant as well as the risk of MTCT transmission of HIV.

Information about the safety of drugs in pregnancy is derived from animal toxicity data, observational experience, registry data and clinical trials. Relatively limited data are available on the

pharmacokinetics and safety of antiretroviral drugs in humans during pregnancy. Table 5 contains information on the USA Food and Drug Administration pregnancy category, placental passage, animal carcinogenicity and teratogenicity studies and breast milk passage, and data from human studies in pregnant women on available antiretroviral drugs. Drugs shown to be effective in reducing MTCT include ZDV, ZDV/3TC and NVP [106-110, 116]. Optimally, ARV regimens for pregnant women should include drugs that have proved effective in reducing transmission. The largest body of experience relating to efficacy and maternal and fetal safety has been gained with ZDV. Consequently, first-line treatment regimens in pregnant women should include ZDV whenever possible. Furthermore, because all regimens of proven prophylactic effectiveness have included intrapartum drug administration, maternal antiretroviral drugs should continue to be given during labour.

Pharmacokinetic studies of ZDV, 3TC, d4T and ddI indicate that the dose used for these drugs during pregnancy should be the same as that used in non-pregnant individuals [117-119]. ABC has not been formally evaluated in pregnant women. Of the NsRTIs that have been studied, all cross the placenta, although at varying rates (Table 5). While placental passage could be associated with a potential for fetal toxicity, it is probably also necessary for the effective prevention of MTCT of HIV. Because ZDV and 3TC are the drugs with which the greatest experience of safety in pregnant women has been gained, and since they have been shown to reduce MTCT, this dual nucleoside component should be the first choice for use in pregnancy.

Reports suggest that lactic acidosis/hepatic steatosis toxicity associated with NsRTI drug therapy may be higher in women receiving d4T than in those given other NsRTIs, and may be of particular concern in pregnant women (Chapter XV, Table 10 and Annex 11) [113, 120-122]. While the frequency of this syndrome in pregnant HIV-infected women receiving NsRTI treatment is unknown, there have been at least three reports of maternal death (two with accompanying fetal death) attributable to severe lactic acidosis in women who received d4T in combination with ddI and an NNRTI or PI for the entire duration of pregnancy [68]. All cases were in women receiving treatment with these agents at the time of conception and throughout pregnancy; the women presented late in pregnancy with symptomatic disease that progressed to death in the immediate postpartum period. Non-fatal cases of lactic acidosis in pregnant women receiving d4T have also been

reported [123]. Consequently, the d4T/ddI dual nucleoside component is not recommended for use in pregnant women with HIV infection unless other regimens have failed or caused unacceptable side-effects.

Providers caring for pregnant women receiving NsRTIs should be alert to early symptoms of lactic acidosis/hepatic steatosis, which can be difficult to differentiate from symptoms of pregnancy itself (Chapter XV, Table 10 and Annex 11).

Mitochondrial dysfunction has been described in some uninfected infants with *in utero* exposure to ZDV/3TC or ZDV alone [124]. Neurological symptoms and lactic acidosis, with death in two severe cases, were the primary significant clinical manifestations. The link between these clinical findings and *in utero* exposure is controversial. Even if it is causal, significant clinical disease or death appear to be extremely rare (<1%) [125-127].

NVP is the only NNRTI that has been studied in pregnancy [128-130]. Standard dosing appears adequate for women in the third trimester; no evaluations have been made of dosage earlier in pregnancy. NVP rapidly crosses the placenta to achieve levels in the fetus similar to those in the mother. EFZ has not been studied in pregnant women but probably undergoes significant transplacental passage. Pregnancy should be avoided in women receiving EFZ because there are concerns related to teratogenicity, as discussed previously, and its use should be avoided during the first trimester. NVP is therefore the NNRTI of choice for use in pregnancy.

PIs have been associated with the development of glucose intolerance and even diabetes mellitus in non-pregnant individuals. Pregnancy is also a risk factor for hyperglycaemia; it is not known whether the use of PIs exacerbates the risk of pregnancy-associated hyperglycaemia. Hyperglycaemia in pregnancy can lead to an increased risk of macrosomia, fetal distress, pre-eclampsia and stillbirth. Symptoms of hyperglycaemia (e.g. increased urination and thirst, weight loss) should be discussed with pregnant women receiving PIs and they should be advised to see their health care provider if such symptoms occur.

RTV, NFV, IDV and SQV have been studied pharmacokinetically in pregnant women and shown to be well tolerated. These PIs underwent minimal or no placental passage. While data on birth defects associated with the use of PIs are too few for conclusions to be drawn, the limited placental passage of the drugs suggests a low risk of teratogenicity. NFV, followed by SQV, are the most common

PIs used to treat pregnant HIV-infected women in resource-rich countries [131]. NFV has been well tolerated by pregnant women and when administered at 1250 mg twice daily it produces adequate drug levels; it is the PI of first choice for use during pregnancy (Table 5, Annex 9) [132, 133]. Phase I studies of SQV and IDV indicate that dosing above the standard level may be required during pregnancy [134-137]; however, the use of low-dose RTV pharmacoenhancement of SQV and IDV should provide adequate drug levels. IDV carries the theoretical risk of exacerbating neonatal hyperbilirubinaemia if used near to or during labour, and is therefore a less desirable PI choice in pregnancy. LPV/r has not been studied in pregnant women.

C. Women first diagnosed with HIV infection during pregnancy

The period when the fetus is most susceptible to potential teratogenic effects of drugs is during the first 10 weeks of gestation. The risks of ART to the fetus during this period are not known. Consequently, women in the first trimester of pregnancy may wish to consider delaying the initiation of therapy until after 10-12 weeks of gestation. The decision to delay the initiation of therapy hinges in part on a consideration of the severity of maternal HIV disease and the potential benefits and risks of delaying initiation for several weeks until completion of the first trimester. ART is rarely initiated because of a medical emergency. However, for women who are severely ill the benefit of early initiation may outweigh the theoretical risk to the fetus. This is particularly true if therapy is begun with drugs for which considerable experience of use in pregnancy has been gained (such as ZDV, 3TC, NVP or NFV).

D. HIV-infected women receiving antiretroviral drugs who become pregnant

For women who become pregnant while receiving ART the options are to suspend therapy temporarily during the first trimester, to continue the same therapy or to change to a different drug regimen. The issues to be considered in making a decision include the stage of gestation, the severity of maternal disease, the tolerance of the regimen in pregnancy and the potential for adverse effects on the fetus.

While many women are not aware of their pregnant state until well into the first trimester, some may know they are pregnant early in gestation, and concern about the fetus may lead some to consider temporarily discontinuing therapy until completion of the first trimester. There is a concern that temporary discontinuation of ART could lead

to a rebound in viral load which might be associated with an increase in the risk of early *in utero* MTCT. However, most cases of MTCT occur late in pregnancy and during delivery; early *in utero* transmission is rare. In order to reduce the potential for the emergence of resistance in the event that it is decided to temporarily discontinue antiretroviral treatment during the first trimester, all drugs should be stopped simultaneously and restarted simultaneously.

A switch in ART during pregnancy should be considered if the drug being received has teratogenic potential (i.e. EFZ), if there are concerns about the risk of severe toxicity to the pregnant woman (e.g. with d4T/ddI), or if there is significant intolerance of the drug that could be compounded by pregnancy (e.g. gastrointestinal intolerance compounded by morning sickness) and lead to poor drug adherence. In women for whom therapy has to be temporarily discontinued because of pregnancy-related hyperemesis, it should not be restarted until sufficient time has elapsed to ensure tolerance of the drugs. If therapy has to be discontinued, all drugs should be stopped simultaneously and restarted simultaneously.

E. HIV-infected women receiving antiretroviral therapy who are breastfeeding

Current WHO/UNAIDS/UNICEF guidelines recommend that women with HIV infection be fully informed of both the risks and benefits of breastfeeding and be supported in their decision about feeding practices. Safe alternatives to breastfeeding may not be available in some resource-limited settings. In such situations, exclusive breastfeeding for the first several months of life is recommended.

Passage into human breast milk has been evaluated for only a few ARV drugs (Table 5). However, in rodent studies, most ARV drugs were excreted into the milk of lactating rats. ZDV, 3TC and NVP have all been detected in the breast milk of HIV-infected women. The use of potent therapy that significantly lowers the maternal plasma viral load could also lower the viral load in breast milk and be associated with a reduced risk of HIV transmission in breast milk. However, if ARV drugs penetrate the breast milk in suboptimal concentrations or if some drugs of the regimen penetrate into the breast milk while others do not, drug levels in the milk may not be sufficient to decrease viral replication. The presence of inadequate drug levels or the penetration of only a single drug into the milk could promote the development of drug-resistant virus in the milk, which could be transmitted to the infant. Moreover, the toxicity

of chronic ARV exposure of infants via breast milk is unknown.

Women who require ART and who are breastfeeding should continue their antiretroviral therapeutic regimen. The efficacy of potent ART in preventing postnatal transmission of HIV through breast milk is not known. A number of international clinical trials are evaluating the effect of such ART on the risk of MTCT in women who do not require therapy for their own health. In these studies, treatment is provided solely for reducing breast-milk transmission and is stopped after weaning. As yet there are no data on the safety and efficacy of this approach.

F. HIV-infected women who have received short-course antiretroviral prophylaxis to reduce mother-to-child transmission and require postpartum treatment

Short-course ARV drug regimens not fully suppressing viral replication which are used to prevent MTCT may be associated with the development of antiretroviral drug resistance. This is most likely to occur with prophylactic regimens using antiretroviral drugs for which a single point mutation can confer drug resistance, such as NVP or 3TC. In the Ugandan HIVNET 012 study of single-dose intrapartum/neonate NVP for prevention of MTCT, 21 of 111 women (19%) receiving single-dose NVP developed detectable NNRTI-associated resistance mutations by six weeks postpartum, most commonly the K103N mutation [138, 139]. The development of resistance was associated with the HIV viral load and CD4 cell count at delivery. In follow-up samples obtained 12-18 months postpartum, resistance mutations were no longer detectable and wild-type virus again predominated. The rapid development of genotypic resistance to 3TC was also observed when 3TC was given as part of a dual NsRTI regimen with ZDV in pregnant women to prevent MTCT. In a study in France, where 3TC was added to ZDV after 32 weeks of gestation, 39% of 132 women had detectable high-level resistance (M184V) to 3TC at six weeks postpartum; resistance was only detected in women who had received 3TC for four weeks or longer during pregnancy [140].

It is not known whether the presence of transient drug resistance to NVP induced by a single dose of NVP or to 3TC with short-course ZDV/3TC prophylaxis might be associated with a diminished virological response to subsequent NNRTI-based or 3TC-based therapy in women who require the initiation of treatment postpartum. Some workers have recommended that a triple NsRTI or a PI-based regimen be substituted for an NNRTI-based regimen for initial therapy in women who have received single-dose NVP prophylaxis during the period that

NVP resistance is likely to be present. However, the dynamics of nevirapine resistance following single-dose prophylaxis have not been defined. In the absence of data indicating an adverse effect, denying the use of an NNRTI-based regimen to women who have received single-dose NVP could significantly limit their treatment options. Further research is urgently needed on the impact of specific drug mutations on future maternal treatment outcomes. Nevertheless, current information suggests that the prior administration of short-course ZDV/3TC or single-dose NVP for the prevention of MTCT should not preclude the use of these agents as part of a combination ARV drug regimen initiated for the treatment of HIV disease in women.

G. Issues related to adherence to therapy in pregnancy and postpartum

Adherence to treatment may be more difficult in pregnant and immediately postpartum women than in non-pregnant individuals [141, 142]. Potential obstacles to adherence that are unique to pregnancy include morning sickness and gastrointestinal upset, which can be further compounded by ARV-associated nausea and fears that antiretroviral drugs might harm the fetus. If the temporary discontinuation of therapy is required for any reason during pregnancy, all drugs should be stopped simultaneously and restarted simultaneously in order to reduce the potential for the emergence of resistance.

The physical changes of the postpartum period coupled with the stresses and demands of caring for a neonate may make adherence to treatment especially difficult after birth. It is important to give particular attention to the provision of additional supports for maintaining adherence to therapy during the antepartum and postpartum periods.

Table 5. Preclinical and clinical data relevant to the use of antiretroviral drugs during pregnancy

Antiretroviral drug	Food and Drug Administration pregnancy category[a]	Placental passage	Long-term animal carcinogenicity studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors			
Abacavir (ABC)	C	Yes (rats)	Not completed
Didanosine (ddI)	B	Yes (human, 50%)	Not carcinogenic in rodent studies
Lamivudine (3TC)	C	Yes (human, 100%)	Not carcinogenic in rodent studies
Stavudine (d4T)	C	Yes (rhesus monkey, 76%)	Bladder and liver tumours in rodents given doses of ≥250 times greater than human exposures

Animal teratogenicity studies	Breast-milk passage	Human studies in pregnancy	Other comments
Anasarca and skeletal malformations in rodents when given in doses 35 times higher than human therapeutic exposure; rabbits receiving 8.5 times human therapeutic exposure did not have fetal malformations	Excreted into breast milk of lactating rats	No data	Serious hypersensitivity reactions, including fatalities, in non-pregnant persons
Not teratogenic in rodent studies	Excreted into breast milk of lactating rats	Studied in 14 women enrolled at ≥26 weeks of gestation and in phase II trial alone or with d4T at ≥28 weeks gestation, well-tolerated	Gastrointestinal side-effects may be a problem in early pregnancy; d4T/ddI used during entire pregnancy may be associated with lactic acidosis/ hepatic steatosis
Not teratogenic in rodent studies	Excreted into breast milk in humans	Used in pregnancy for treatment; effective in reducing perinatal transmission; no increased birth defects seen	M184V mutation seen in 39% of pregnant women receiving AZT/3TC alone ≥4 weeks antepartum
Not teratogenic in rodent studies, but sternal bone calcium decreases at high dose	Excreted into breast milk of lactating rats	Studied in small number of women enrolled at ≥14 weeks of gestation, and phase II trial alone or with d4T ≥28 weeks gestation, well-tolerated	d4T/ddI use during entire pregnancy may be associated with lactic acidosis/ hepatic steatosis

Antiretroviral drug	Food and Drug Administration pregnancy category[a]	Placental passage	Long-term animal carcinogenicity studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors			
Tenofovir disoproxil fumarate (TDF)	B	Yes (rat and monkey)	Not completed
Zidovudine (ZDV)	C	Yes (human, 85%)	Non-invasive vaginal epithelial tumours in rodents; lung, liver, vaginal tumours in mice exposed *in utero* to doses 25-50 times greater than human exposure
Non-nucleoside reverse transcriptase inhibitors			
Efavirenz (EFZ)	C	Yes (cynomologus monkey, rat, rabbit, 100%)	Not completed
Nevirapine (NVP)	C	Yes (human, 100%)	Not completed

Animal teratogenicity studies	Breast-milk passage	Human studies in pregnancy	Other comments
Not teratogenic in rodent studies, but severe osteomalacia when given to juvenile animals at high doses	Excreted into breast milk of lactating rats	No data	
Rodent studies demonstrated maternal toxicity and fetal malformations when given in almost lethal doses that were 350 times the dose given to humans	Excreted into breast milk in humans	Extensive study in human pregnancy and neonates; effective in reducing MTCT; no increased birth defects seen	Extensive clinical data on safety and efficacy during pregnancy; follow-up in infants aged up to 6 years with *in utero* exposure shows no adverse effects
Anencephaly, anophthalmia, microophthalmia, cleft palate in 3 of 20 cynomologus monkeys with *in utero* exposure	Unknown	One infant reported with myelomeningocele with *in utero* exposure to EFZ during first trimester	Because of potential for teratogenicity, should be avoided in women who may become pregnant and during pregnancy (first trimester)
Not teratogenic in rodent studies	Excreted into breast milk in humans (median concentration ~76% serum levels)	Used in pregnancy for treatment; effective for reducing perinatal transmission given as single dose to mother and baby	K103N mutation seen at six weeks postpartum in 19% of pregnant women receiving single-dose intrapartum nevirapine, not found at 12 months postpartum

Antiretroviral drug	Food and Drug Administration pregnancy category[a]	Placental passage	Long-term animal carcinogenicity studies
Protease inhibitors			
Indinavir (IDV)	C	Minimal (human)	Not completed
Lopinavir/ ritonavir (LPV/r)	C	Unknown	Not completed
Nelfinavir (NFV)	B	Minimal (humans)	Not completed

Animal teratogenicity studies	Breast-milk passage	Human studies in pregnancy	Other comments
Extra ribs in rodents; unilateral anophthalmia in 3% of rats exposed *in utero*; hyperbilirubinaemia in neonatal rhesus monkeys increased fourfold with administration after birth (not with only *in utero* exposure)	Excreted into breast milk of lactating rats at levels above maternal plasma level	Studied in small number of pregnant women; antepartum drug levels lower than postpartum levels	Requires administration with low-dose ritonavir boost to achieve adequate levels in pregnancy; use is limited because of concerns about hyperbilirubinaemia and nephrolithiasis
Not teratogenic in rodent studies, but embryotoxic and delayed skeletal ossification and increase in skeletal variations in rats with lopinavir drug exposure ~0.7-fold and for ritonavir 1.8-fold that in humans; not seen in rabbits	Excreted into breast milk of lactating rats	No data	
Not teratogenic in rodent studies	Excreted into milk of lactating rats	Studied in small number of pregnant women; dose regimen of 1250 mg twice daily needed for adequate levels	Most experience in pregnant women; dose regimen of 1250 mg twice daily required to achieve adequate levels in pregnancy

Antiretroviral drug	Food and Drug Administration pregnancy category[a]	Placental passage	Long-term animal carcinogenicity studies
Protease inhibitors			
Ritonavir (RTV)	B	Minimal (human)	Liver adenomas and carcinomas in male mice at doses about four times above those of human exposure; no effect in female mice
Saquinavir (SQV)	B	Minimal (human)	Not completed

[a] The FDA pregnancy categories are as follows.

A Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).

B Animal reproduction studies fail to demonstrate a risk to the fetus; adequate and well-controlled studies of pregnant women have not been conducted.

C Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted; the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.

Animal teratogenicity studies	Breast-milk passage	Human studies in pregnancy	Other comments
Not teratogenic in rodent studies, but developmental toxicity with ossification delay and skeletal malformations with exposure at ~30% of human exposure; cryptorchidism in rodents at 22% of human exposure	Excreted into milk of lactating rats	Studied in small number of pregnant women; antepartum drug levels lower than postpartum levels	Gastrointestinal intolerance may limit use as full-dose sole protease inhibitor during pregnancy and higher dose may be required for adequate levels; therefore use limited to low-dose boosting of saquinavir, indinavir and lopinavir
Not teratogenic in rodent studies	Excreted into milk of lactating rats	Studied in small number of pregnant women; standard dose resulted in inadequate drug levels; current dose under study, 800 mg saquinavir in combination with 100 mg ritonavir given twice daily	Requires administration with low-dose ritonavir boost to achieve adequate levels in pregnancy

D Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug in pregnant women clearly outweighs any possible benefit.

XI. INFANTS AND CHILDREN

Although the pathogenesis of HIV and the underlying principles of ART are similar in adults and children, there are specific physiological, clinical, practical and social issues to consider when treating HIV-infected children with ART. Data on the efficacy of ARVs in adults can generally be extrapolated to children, but issues of pharmacokinetics, formulations and ease of administration require special consideration. There are also difficulties in making a laboratory diagnosis of HIV infection in infants born to HIV-positive women in most resource-poor settings, as all babies have maternal antibodies up to the age of 12-18 months, and clinical definitions of HIV infection lack both sensitivity and specificity in this age group. Differences from adults in the natural history of HIV and in the predictive value of surrogate markers impact on decisions about starting and switching ART. Suitable formulations for children are not available for some ARVs, particularly the protease inhibitors. Moreover, as young children metabolize drugs differently from adults, data on the pharmacokinetics in a particular age group must be available if a drug is to be used for that age group. There is a particular need for data relating to children aged under 2-3 years.

In this chapter, differences in HIV between adults and children and their impact on the management of ART are discussed. Special attention is given to the timing of the introduction of ART, the most appropriate ART regimens for children in resource-limited settings, and monitoring. As a general principle, the ARV regimen that the parents or guardians are or will be taking should also be taken into consideration when deciding on the most appropriate regimen for a child. The availability of a suitable formulation and the simplicity of the dosage schedule are important in determining the initial choice of ART for children.

A. Differences in HIV infection between adults and children

1. Diagnosis of HIV in babies born to HIV-infected women

Most children in resource-limited settings acquire HIV from their mothers around the time of delivery or during breastfeeding. However, because all babies born to HIV-infected women have maternal antibodies until they are up to 15-18 months of age (median 10 months, HIV antibody tests cannot be used for

diagnosis of HIV infection in infants until after this age. Early definitive diagnosis requires the use of assays that detect the virus or its components, such as the HIV DNA polymerase chain reaction (PCR) or assays to detect plasma HIV RNA or immune-complex-dissociated (ICD) p24 antigen. Detection of HIV DNA by PCR is the gold standard diagnostic test but lacks sensitivity in the first weeks of life, as do plasma HIV RNA assays. The ICD p24 antigen assay, although specific and less costly, lacks sensitivity, and therefore a negative p24 antigen assay does not exclude infection.

If HIV DNA PCR or RNA assays are available the preferred time of the first test for identifying babies infected in utero or at delivery is when they are about 2-3 months of age; test sensitivity is close to 100% at this time [143]. However, it could be argued that testing at this time in resource-poor settings is not useful or cost-effective unless the early initiation of ART is being considered. Furthermore, if an infant is being breastfed a negative virological test at the age of 2-3 months does not exclude infection because the risk of HIV transmission continues throughout breastfeeding. In such an infant, once breastfeeding has ceased and if the child is aged over 18 months an HIV antibody test alone can be used to diagnose infection. Although there are cost constraints, it would be reasonable, if DNA or RNA assays were available, to use the assay only to confirm HIV infection in an infant with symptoms suggestive of HIV infection and for whom ART is therefore being considered. It is recognized that, in most resource-poor settings, early definitive diagnosis is not possible at present, and cheaper reliable tests are urgently required.

2. *Use of markers (CD4 cell count, HIV-1 RNA viral load and growth monitoring) as surrogates of HIV disease progression, and markers of response to therapy in children*

HIV-1 RNA viral load is an independent predictor of progression to AIDS or death in HIV-infected children, as it is in adults [144,145]. However, plasma HIV RNA levels are very high in infants (e.g. several million copies/ml) and they persist at high levels for much longer than in infected adults following primary infection (e.g. years rather than months) [146]. Particularly in young children, the plasma HIV RNA level has a low predictive value for subsequent disease progression and mortality [144-146]. Viral load therefore has played a lesser role in decisions about starting ART in young children than in adults. In developed countries there is currently no agreed viral load cut-off for starting ART in children.

CD4 cell counts in children without HIV infection are comparatively high and more variable in young children and they decline with age, not reaching adult values until the age of about 6-8 years [147]; the CD4 cell percentage is less variable, although it also decreases with age. It is therefore preferable to use the CD4 cell percentage instead of the absolute count for decision-making on ART for HIV-infected children aged under 8 years. As with HIV RNA levels, the predictive value of the CD4 cell percentage for AIDS or death is low in young children [145]. For example, the CD4 cell percentage and count are poor predictors of the development of *Pneumocystis carinii* pneumonia (PCP) in infants [148]. Cotrimoxazole prophylaxis has therefore been recommended in developed countries for all infants born to HIV-infected women from the age of 4-6 weeks to that of 12 months. Increasing recognition of PCP as a significant cause of mortality in infected children in resource-poor countries has led to recommendations that cotrimoxazole prophylaxis be given to all children up to the age of 6-12 months born to HIV-infected women. The predictive value of the CD4 cell percentage for disease progression or death improves considerably after children are 2 years of age [145].

With potent ART, children may have a greater increase in CD4 cell numbers than adults, even in the absence of virological suppression, because the thymus is more active [149]. Immune reconstitution may therefore be more robust in infected children receiving ART than in infected adults.

B. When to start antiretroviral therapy in children

In developed countries, cohort studies have indicated that about 20% of HIV-infected infants progress to AIDS or death by 12 months of age, and that a substantial contribution to mortality is made by PCP in infants aged under 6 months who are not receiving cotrimoxazole. Cohort studies have also indicated that 40-50% of vertically infected children survive without ART until they are 9-10 years of age[150]; some children may not require ART until adolescence or early adult life. In developed countries there is limited experience showing that potent ART, started during the first months of life, may result in prolonged virological suppression and the retention of normal immune function in some infants, although they remain HIV DNA PCR-positive [151]. In the USA these data have led to an aggressive approach involving the early initiation of potent ART in infected infants. However, while it is theoretically possible that early therapy during primary infection in infants, even for a limited period, may change the long-term outcome of the

disease, this has not been evaluated in clinical trials. There remain concerns about the potential consequences of the loss of HIV-specific immune responses in infants receiving potent ART as well as about the ability of carers to administer long-term therapy to asymptomatic children; a lack of adherence could lead to virological rebound and resistance to ARVs [151,152]. Clinical practice varies: United States guidelines are relatively aggressive and European guidelines are relatively conservative with regard to the early initiation of ART [153, 154].

In Africa, mortality caused by HIV infection in young children is much higher than in developed countries, approaching 40% or more by the age of 2 years [155, 156]. While this might argue for the early initiation of potent ART, further research is needed before such recommendations can be made. Additionally, the lack of diagnostic assays that can identify HIV infection in children aged under 18 months in resource-limited settings poses a significant problem if the early initiation of ART is a goal. At present it is not clear whether the potential virological and immunological benefits of early initiation in asymptomatic young infants outweighs the potential problems, such as the need for early diagnosis of HIV infection, the limited data on ARV pharmacokinetics in infants making dosing recommendations difficult, the potential for long-term toxicity, and the difficulties with adherence to therapy, particularly because children must rely on carers for drug administration.

Acute infections should generally be treated before ART is begun; CD4 cell measurements, when available, should be performed after resolution of the acute infection. Tuberculosis is often presumptively diagnosed in children in resource-poor countries because of general difficulties of diagnosis in children; in HIV-infected children being treated for proven or presumptive tuberculosis, ART should generally be deferred until antituberculous therapy has been in progress for at least two months, and, if deemed safe, until the completion of all antituberculous therapy. This is to avoid interactions with rifampicin and possible decreased adherence to ART and tuberculosis medications because of the number that have to be administered. If an HIV-infected child with tuberculosis has significant HIV symptoms and/or severe immunodeficiency and requires the initiation of ART, the considerations about the choice of regimen are similar to those for adults, and include a triple NsRTI regimen or a regimen of two NsRTIs and efavirenz (EFZ), an NNRTI, in children aged over 3 years (see also Chapter XII).

1. Starting potent ART in infancy (<18 months of age)

All infants born to HIV-infected mothers should be followed up, fully immunized and given nutritional support. They should all receive cotrimoxazole prophylaxis, at least for the first six months and preferably for the first 12 months of life in order to prevent PCP. If an infant becomes symptomatic, virological testing should be performed, if available, in order to determine the HIV infection status.

a. Infants with virological diagnosis of HIV infection

ART is recommended for infants under 18 months of age for whom there is virological documentation of HIV infection and in whom there is WHO paediatric stage III disease (AIDS-defining opportunistic infections, severe failure to thrive, progressive encephalopathy, malignancy, recurrent septicaemia or recurrent meningitis), irrespective of the CD4 cell percentage or CD4 cell assay availability (Table 6, Annex 2). ARV treatment may also be considered in this circumstance for infants with advanced WHO paediatric stage II disease (severe symptoms short of an AIDS-defining event, such as severe persistent or recurrent candidiasis outside the neonatal period, weight loss, fevers, and recurrent severe bacterial infections). If CD4 cell assays are available, ART may also be considered for children aged under 18 months with virologically proven infection and in whom there is WHO paediatric stage I (asymptomatic) or stage II disease and a CD4 cell percentage below 20%, particularly if it is decreasing. The initiation of ART is not recommended in asymptomatic HIV-infected infants under 18 months of age in the absence of the ability to perform CD4 cell assays.

b. Infants with no virological HIV diagnosis

Many of the clinical symptoms in WHO paediatric stages II and III are not specific for HIV infection and significantly overlap those of illnesses seen in many uninfected children in resource-limited settings. They cannot, therefore, be viewed as diagnostic of HIV infection. Consequently, in the absence of a definitive diagnosis of HIV infection by means of a virological assay, HIV-exposed infants under 18 months of age should not be considered for ART if CD4 cell assays are not available, regardless of the clinical symptomatology. However, if CD4 cell assays are available, infants who are HIV antibody-seropositive, have had an AIDS-defining illness (WHO paediatric stage III disease), and in whom the CD4

cell percentage is below 20%, may be considered for ART even if virological testing is not available (Table 6). HIV antibody testing must be repeated at the age of 18 months in order to confirm the diagnosis of HIV infection; ART should be continued only in children remaining HIV antibody- positive.

2. Starting potent ART in children aged 18 months or more

Among children aged 18 months or more, ART is recommended for those with a positive HIV antibody test and WHO paediatric stage III disease, regardless of the CD4 cell percentage or the availability of CD4 cell assays (Table 6). ARV treatment may also be considered in this circumstance for children with advanced WHO paediatric stage II disease. When CD4 assays are available, ART should be considered in HIV-seropositive children aged 18 months or more with WHO paediatric stage I (asymptomatic) or stage II disease and in whom the CD4 cell percentage is below 15%, particularly if it is declining. Preliminary data on the predictive value of total lymphocyte counts in a cohort of 376 symptomatic HIV-infected children of mean age 3.5 years in the USA indicate that a total lymphocyte count below 2500 cells/mm^3 is associated with an elevated risk of mortality and might be considered as an indicator of immunodeficiency if CD4 assays are not available, although further data are needed before this can be routinely recommended [157]. For children aged 8 years or more an absolute CD4 cell count of less than 200/mm^3 can also be used as an indication for ART.

Table 6. Recommendations for initiating antiretroviral therapy in children

CD4 testing	Age	HIV diagnostic testing
If CD4 testing is available	<18 months	Positive HIV virological test[a]
		HIV virological testing not available but infant HIV seropositive or born to known HIV-infected mother (Note: HIV antibody test *must* be repeated at 18 months of age to obtain definitive diagnosis of HIV infection)
	≥18 months	HIV antibody-seropositive
If CD4 testing is not available	<18 months	Positive HIV virological test
		HIV virological testing not available but infant HIV seropositive or born to mother known to be HIV-infected
	≥18 months	HIV antibody-seropositive

[a] HIV DNA PCR or HIV RNA or immune-complex-dissociated p24 antigen assays.

[b] Initiation of ARV can also be considered for children who have advanced WHO paediatric stage II disease including, for example, severe recurrent or persistent oral candidiasis outside the neonatal period, weight loss, fevers, or recurrent severe bacterial infections, irrespective of the CD4 count.

[c] The rate of decline in the CD4 percentage (if measurement available) should be factored into the decision-making process.

Treatment recommendation
WHO paediatric stage III (AIDS), irrespective of CD4 cell percentage[b] WHO paediatric stage I disease (asymptomatic) or stage II disease with CD4 percentage <20%[c]
WHO paediatric stage III disease (AIDS) with CD4 cell percentage <20%
WHO paediatric stage III disease (AIDS) irrespective of CD4 cell percentage[b] WHO paediatric stage I disease (asymptomatic) or stage II disease with CD4 percentage <15%[c]
WHO paediatric stage III[b]
Treatment not recommended[d]
WHO paediatric stage III[b]

[d] 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; in the absence of virological testing and CD4 cell assay availability, therefore, HIV-exposed infants under 18 months of age should generally not be considered for ART, regardless of their symptoms.

C. Antiretroviral therapies for children

Most ARVs available for adults are also available for children. Some have formulations appropriate for young children who cannot take tablets or capsules (Annex 10). All the recommended NRTIs for adults (ZDV, 3TC, d4T, ddI and ABC) have formulations appropriate for young children. However, combination ZDV/3TC and ZDV/3TC/ABC are only available in tablet formulations. d4T and ZDV liquid formulations require large volumes; d4T liquid must be refrigerated, ZDV liquid is light sensitive, and both require storage in glass bottles, which must be brown in the case of ZDV. ABC and 3TC are both relatively low-volume liquids (requiring identical volumes) with a reasonable taste; a recent report suggested that they could be a potent NsRTI combination backbone for HAART in children [158].

For NNRTIs, only NVP has a licensed liquid formulation; an EFZ liquid formulation is not yet available commercially in many countries. NVP can be used for children of all ages, while EFZ should be used only for those aged over 3 years because of the lack of pharmacokinetic data for younger children.

Among the PIs there are considerable problems with appropriate formulations and/or adequate pharmacokinetic data in young children for all drugs except NFV and LPV/r. NFV powder is difficult to use and crushed tablets are preferable; pharmacokinetic data indicate that the dose of NFV required to achieve therapeutic concentrations in children aged under 2 years is significantly higher than that for older children and adults. LPV/r liquid can be used in children who weigh over 10 kg but the pharmacokinetic data relating to infants are limited. Other RTV-boosted PI regimens, such as IDV/r or SQV/r, pose a problem in younger children because IDV and SQV are not available in formulations appropriate for children, and RTV liquid is not palatable. However, IDV/r and SQV/r can be used for older children or adolescents who can swallow capsules and for whom the current capsule formulations allow dosing to be calculated on the basis of body weight or surface area and among whom adherence can be assured.

1. Metabolism of ARVs in children

Drug metabolism in children varies with age, and pharmacokinetic data are not available for all ARV drugs, particularly in respect of children under 2 to 3 years of age (Annex 10). In general, children metabolize NNRTI and PI drugs faster than adults and require doses

higher than the equivalent ones for adults in order to achieve appropriate drug levels. In addition, variation in pharmacokinetic parameters between and within individuals is frequently greater in children than in adults.

2. ARV formulations for children

It is necessary to consider the availability of suitable formulations of ARV drugs that children can take in appropriate doses. Medicines have to be administered by a parent or guardian, and issues of palatability are of particular importance in young children because the refusal or spitting out of medications can lead to major difficulties with adherence and appropriate dosing. Additionally, liquid formulations may not be easily available. Even if they are, they may be comparatively expensive in resource-poor settings. Moreover, there are difficulties with the storage and shelf-life of liquid ARV preparations (Annex 10).

It is important to stress that where tablets or capsules are available in low enough doses to enable accurate dosing for children of most ages, e.g. d4T capsules of 15, 20 and 30 mg or NFV scored tablets that can be halved, the use of tablets requiring to be cut up (particularly unscored tablets) is not recommended because underdosing or overdosing is possible. This can lead to an increased risk of resistance or toxicity, and the dose cannot be easily adjusted as a child grows. Some drug combination tablets (e.g. fixed-dose ZDV/3TC) do not have the ZDV and 3TC components evenly distributed and therefore cutting them is not recommended.

3. ARV dose calculations for children

ARV drugs for children may be approved at doses that are calculated either as milligrams per kilogram of body weight or milligrams per square metre of body surface area. Standardization is important so that non-expert personnel can safely dispense correct doses. It is therefore desirable to provide health workers with a table of drug doses that can be administered according to weight bands. Drug doses have to be increased as a child grows; otherwise there is a risk of underdosage and the development of resistance.

4. Consideration of therapies used to reduce mother-to-child transmission of HIV infection

If a mother has received ART during pregnancy, either to reduce MTCT or for her own disease, there is a possibility that she may

transmit resistant virus to her baby if the baby also becomes infected. Additionally, resistance could be induced de novo in the infant if the infant is infected in utero and then exposed to an antiretroviral drug being used for prophylaxis before the infection status is known. This problem arises particularly if NVP or 3TC has been used as part of a non-suppressive regimen, because resistance to these drugs can be induced rapidly by a single point mutation.

It is not known whether ARV choices for infants who have been exposed to non-suppressive ARV regimens used to prevent MTCT should be modified (see Chapter X). Further research is needed on the efficacy of first-line potent ART treatment regimens containing NVP or 3TC for infants who are infected despite prophylaxis involving the use of these drugs. In the meantime, prior administration of short-course ZDV/3TC or single-dose NVP should not preclude the use of these drugs within combination antiretroviral drug regimens for the treatment of HIV-infected children, particularly those in whom therapy begins at 12 months of age or older, when wild-type virus is likely to predominate.

5. Choice of first-line regimens in children

The choice of first-line ART for children follows the same principles as in adults, with additional considerations about pharmacokinetic data and formulations available for children (Table 7, Annex 10). The limited studies of ART in children suggest that broadly similar improvements are seen in surrogate markers with many different drug regimens. Although the data are limited, there could be advantages in starting therapy using the triple NsRTI regimen of ABC, ZDV and 3TC because of the frequency of suspected, empirically treated or proven tuberculosis disease in HIV-infected children in resource-limited settings and the lack of interactions of this combination of ARVs with antituberculous medications.

Other first-line choices for children would be two NsRTIs plus NVP for children under 3 years of age or under 10 kg or with EFZ for older children or those over 10 kg (Table 7). EFZ would be the NNRTI of choice in children on rifampicin if ART had to be started before antituberculous therapy was completed.

6. Monitoring and when to change therapy

Important clinical signs of response to antiretroviral therapy include improvement in growth in children who are failing to grow, improvement in neurological symptoms and development in

Table 7. Recommended first-line antiretroviral regimens for children[a]

Regimen	Comments
ZDV/3TC[b] plus ABC	Preferred if concomitant antituberculous therapy is being received
ZDV/3TC[b] plus NNRTI	NNRTI choice: if <3 years or <10 kg, NVP if ≥3 years or ≥10 kg, NVP or EFV

[a]Country-specific considerations and preferences should determine which regimen or regimens to make available.
[b]ZDV/3TC is the first choice dual NsRTI regimen for children as the largest amount of clinical experience has been gained with this one. Other dual NsRTI components can be substituted for children, including ZDV/ddI, d4T/3TC, d4T/ddI and ddI/3TC. ZDV and d4T should never be used together because of proven antagonism.

children demonstrating delay in developmental milestones or encephalopathy, or decreased frequency of infections (bacterial infections, oral thrush, and/or other opportunistic infections) [159]. Clinical monitoring in children should therefore include weight and height growth, developmental milestones and neurological symptoms. Height and weight, which should be assessed with the help of growth charts, may be the most important indicators in the absence of CD4 cell assays. The monitoring of plasma HIV RNA levels is not considered essential and is probably less useful in young children than in adults.

The principles on which to base changes in therapy for children are similar to those applied where adults are concerned. In children, important clinical signs of antiretroviral drug failure include: a lack of growth response to treatment or a decline in growth among children who show an initial growth response to therapy; a loss of neurodevelopmental milestones or the development of encephalopathy; and the recurrence of infections, such as oral candidiasis that is refractory to treatment.

In areas where CD4 cell assays are available, the definition of immunological failure suggesting a need to change therapy includes a return of the CD4 cell percentage to or below the pre-therapy baseline. Because the CD4 cell count, and, to a lesser extent,

the CD4 percentage, normally decline with age in children until they reach adult levels at the age of about age 8 years, CD4 cell decline is difficult to use in assessing the failure of therapy in younger children. However, for children aged 8 years or more a confirmed fall of at least 30% in the CD4 cell count or percentage from the peak value observed after 6 months or more of ART can be used as a potential indicator of treatment failure, as in infected adults.

7. Choice of second-line regimens in children

Because of issues related to palatability and a lack of pharmacokinetic information on drug dosage in younger children, PIs are best kept as second-line therapies for children (Table 8, Annex 10). NFV is the protease inhibitor most used in children. However, the dose requirement is high, especially in children aged under 2 years, and the powder formulation is very hard to use. While not ideal, NFV tablets may be crushed for administration to young children and halved for use in infants, and they may be given 2 or 3 times daily with high-fat foods such as yogurt; unequal dosing may be necessary e.g. half a tablet in the morning, half at lunch time, and a whole tablet in the evening. LPV/r syrup is an excellent potent alternative but it requires refrigeration, has a bitter taste, and the capsules are very large. IDV and SQV are only available in capsule form and are therefore only appropriate for older children or adolescents and should be used with low-dose RTV boosting when given to them. IDV is not ideal for children because of the difficulty of ensuring that large volumes of liquid are drunk in order to avoid the complication of renal calculi.

Table 8. Recommended second-line antiretroviral regimens for children

First-line regimen	Second-line regimen	Alternative second-line regimen
ZDV/3TC/ABC	d4T/ddI/LPV/r[a] or d4T/ddI/NFV or d4T/ddI/NNRTI[b]	d4T/ddI/NNRTI[b] plus either LPV/r[a] or NFV
ZDV/3TC/NNRTI	d4T/ddI/LPV/r[a] or d4T/ddI/NFV	

[a]For children who can swallow capsules and for whom the current capsule formulations allow appropriate dosing calculated on the basis of body weight or body surface area, additional options include SQV/r and IDV/r.

[b]NNRTI choice: if <3 years or <10 kg, NVP; if ⩾3 years or ⩾10 kg, NVP or EFV.

XII. TUBERCULOSIS AND OTHER HIV-RELATED CONDITIONS

A. Tuberculosis

Many patients who are candidates for ART have active tuberculosis (TB). In some areas of sub-Saharan Africa, over two-thirds of patients with active TB are coinfected with HIV [160]. In addition, patients already receiving ART may develop TB. For these reasons, antiretroviral regimens that are compatible with TB therapy should be included in country-specific programmes.

From the global public health perspective the effective treatment and control of TB must remain a central priority when treatment strategies for coinfected patients are being developed [161]. TB is a leading cause of death among HIV-infected patients. WHO estimated that TB accounted for 30% of AIDS-related deaths in 1999 [162]. The management of HIV and TB coinfection is complicated because some antiretroviral agents produce unacceptable drug interactions with antituberculous agents and can magnify the toxicity of TB treatments [163-165]. The introduction of ART must therefore be coordinated with TB programmes so that the success of treatment in established TB programmes is not diminished.

When should ART begin and which regimen should be used for patients with HIV and TB? These are the two major clinical management issues in this area. Tuberculosis treatment with directly observed therapy (DOT) should be initiated promptly in diagnosed cases of TB. There are few data to guide the recommendation as to when to start ART during TB therapy. Delaying ART until TB treatment is completed simplifies the management of coinfected patients because standard regimens for both diseases can be utilized and there is less drug toxicity. In addition, patients who are newly diagnosed with HIV infection can prepare for a commitment to ART. However, it must be emphasized that delaying ART can result in HIV- related comorbidity and even death in patients with low CD4 cell counts [166]. Until more information is available the initiation of ART is recommended for TB patients at very high risk for HIV disease progression and mortality, i.e. a CD4 count below 200 cells/mm^3 or extrapulmonary TB (Table 9).

For patients who develop TB with CD4 counts in the 50-200 cells/mm^3 range or, in the absence of CD4 testing, who have total

lymphocyte counts below 1200 cells/mm^3, ART should be started after TB therapy has been tolerated for two months because the toxicity of TB treatment is greatest during this period (Table 9). In the subset of patients with very low CD4 cell counts (under 50 cells/mm^3) or with other severe HIV disease, two months is probably too long to wait because of the high risk of HIV-associated events [166]. ART should be started in these patients as soon as TB therapy is tolerated. Because drug resistance and treatment failure are possible for both TB and HIV in this setting, experienced clinical staff should be involved in the care of these patients.

There are four ARV options for patients receiving a rifampicin-based TB regimen (Table 9). Triple NsRTI regimens (including ABC) involve no drug interactions with antituberculous therapy and require no dose adjustments. The fixed-dose combination of ZDV/3TC/ABC also has the advantage of a reduced pill burden. However, it is important to note that the hypersensitivity reaction associated with ABC overlaps clinically with the immune reconstitution syndrome (see below) seen with tuberculosis. Consequently, ARV treatment could prematurely and unnecessarily be discontinued in patients with TB who initiate an ARV regimen containing ABC. Other triple NsRTI regimens not including ABC, e.g. ZDV/ddI/3TC, may also be considered, but antiviral potency may be less and peripheral neuropathy and hepatotoxicity may complicate management.

ZDV(or d4T)/3TC/EFZ is another option for patients receiving rifampicin. Although levels of EFZ are reduced in the presence of rifampicin, preliminary pharmacokinetic studies indicate that a daily dose of 800 mg of EFZ may compensate for the enzyme-inducing effects of rifampicin [167]. More data are needed, however, before a definite recommendation about the EFZ dose can be made. The use of EFZ is not recommended for women of childbearing age who may become pregnant. NVP is advised only in patients without other options because rifampicin reduces drug exposure to nevirapine by 31%, and dose adjustments for NVP coadministered with rifampicin have not been established [168]. There is, moreover, theoretical concern about combined hepatotoxicity of NVP and TB medications.

The only recommended PI-containing combination for patients receiving rifampicin is ZDV/3TC/SQV/r or d4T/3TC/SQV/r. There is very limited published information, but data emerging from clinical trials support this choice [169]. The use of other PIs (NFV, IDV/r, LPV/r) is contraindicated because rifampicin induces hepatic

enzymes that reduce exposure to the protease inhibitors to subtherapeutic levels. This interaction is less pronounced for some protease inhibitors with rifabutin, a semisynthetic derivative of rifampicin [163]. However, while rifabutin appears efficacious for the treatment of TB, it is not generally available in resource-limited settings. For a patient already receiving ART when TB develops the regimen should be adjusted so that it is compatible with TB treatment. Following the completion of antituberculous therapy the ART regimen can be continued or changed in accordance with the clinical and immunological status of the patient.

Table 9. Antiretroviral therapy for individuals with tuberculosis coinfection

Situation	Recommendations
Pulmonary TB and CD4 count <50/mm^3 or extrapulmonary TB	Start TB therapy. Start one of these regimens as soon as TB therapy is tolerated: · ZDV/3TC/ABC · ZDV/3TC/EFZ · ZDV/3TC/SQV/r · ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/mm^3 or total lymphocyte count <1200/mm^3	Start TB therapy. Start one of these regimens after two months of TB therapy: · ZDV/3TC/ABC · ZDV/3TC/EFZ · ZDV/3TC/SQV/r · ZDV/3TC/NVP
Pulmonary TB and CD4 >200/mm^3 or total lymphocyte count >1200/mm^3	Treat TB. Monitor CD4 counts if available. Start ART as indicated in Table 3.

The large number of patients with both HIV and TB presents a theoretical opportunity to integrate the delivery of care for these two diseases [162]. While compelling arguments exist for and against this strategy, the current TB infrastructure is unlikely to have the capacity to absorb the HIV population without the infusion of significant resources. At the least, however, there must be cooperation and communication among TB and HIV physicians in order to ensure that compatible treatments are delivered in the optimal fashion.

B. Other opportunistic infections and hepatitis

Patients who develop other opportunistic infections should be treated with ARVs. In contrast to the situation with TB, drug interactions with standard ARV regimens do not pose a significant problem. Drug tolerance and adherence may be reduced in patients being treated for an opportunistic infection who initiate ART. Because of limited hospital inpatient facilities and staff it may be advisable to initiate ART in the outpatient setting after treatment of the acute phase of an infection. The prompt initiation of ART should be considered when opportunistic infections occur for which treatment is not available or for which it is suboptimal, because improvement of the immune system may enhance recovery [170].

Patients coinfected with hepatitis B or C can be safely treated with several ARV regimens [171]. Because of the possibility of additive hepatoxicity, regimens with ddI/d4T and/or NVP should be avoided in patients known to have active hepatitis. 3TC and TDF are both active against hepatitis B and may even have a protective effect against new infections [172, 173]. Patients receiving 3TC or TDF who are known to have hepatitis B and experience ARV regimen failure may wish to continue these medications when the ARV regimen is switched.

C. Immune reconstitution syndrome

For many opportunistic infections, including TB, there can be a transient worsening of infection 2-3 weeks after the initiation of ART. This is called the immune reconstitution syndrome [174, 175]. For patients with TB, this syndrome has been reported to occur in as many as 30% of cases in the developed world [176]. The syndrome is characterized by fevers, lymphadenopathy, worsening pulmonary lesions and expanding lesions of the central nervous system (CNS). These reactions are typically self-limiting, although they may require the use of a brief course of corticosteroids in order to reduce inflammation for CNS or severe respiratory symptoms. The initiation of ART can also unmask previously undiagnosed infections by augmenting the inflammatory response. In general, ART should not be interrupted if the immune reconstitution syndrome occurs.

D. Opportunistic infections and tuberculosis prophylaxis

ART is the most effective approach to reducing the incidence of opportunistic infections in HIV-infected patients but it should not

replace efforts to provide antimicrobial prophylaxis [5]. Co-trimoxazole reduces the risk for bacterial infections, *Pneumocystis carinii* pneumonia and toxoplasmosis and is recommended for all patients who meet the indications for ART [107, 177]. In areas with a high prevalence of cryptococcal disease, fluconazole prophylaxis should be considered for patients with fewer than 100 CD4 cells/mm^3. On the basis of observations made in developed countries, patients responding to ART with a sustained elevation in CD4 cell counts above 200 cells/mm^3 for 3-6 months may be able to discontinue prophylaxis for some opportunistic infections [177].

Preventive therapy for TB, i.e. treatment of latent TB, reduces the risk for active TB in HIV-infected patients, although the durability of this effect may be limited by high rates of reinfection with TB [178-181]. Preventive therapy for TB may not be feasible in many resource-limited settings because of the difficulty in excluding active disease. TB preventive therapy is therefore recommended in areas where diagnostic testing, such as Chest X-Rays, can exclude active TB and where PPD skin testing is feasible. In this circumstance, isoniazid therapy (with pyridoxine supplementation) for 6 months is recommended for reactors to the tuberculin skin test.

XIII. INJECTING DRUG USERS

There may be as many as 2-3 million past and current injecting drug users (IDUs) living with HIV/AIDS. In many countries, therefore, IDUs represent a significant proportion of the persons needing ART. The dual epidemic of injecting drug use and HIV particularly affects resource-poor countries where there is limited access to HIV prevention measures, e.g. needle and syringe exchange programmes.

It has been consistently reported that individuals who report past or current injecting drug use have less access to ART than non-injectors with HIV infection. In many countries they may be generally excluded from ART. It should be further acknowledged that IDUs in resource-poor settings are doubly marginalized and that, as in developed countries, they often encounter significant stigmatization and discrimination. The situation is often worsened by the criminalization of injecting drug use, which can further impede access to appropriate HIV treatment and care, particularly in custodial settings. When appropriate ART is administered, IDUs with HIV infection fare as well as non-drug users with regard to delays in the progression of HIV disease [182-184]. For this reason, IDUs should have the same access to ART as the rest of the HIV-positive population in any country.

A. Adherence to antiretroviral therapy by injecting drug users

1. Lifestyle instability

Lifestyle instability associated with injecting drug use can disrupt adherence to ART. However, it should be noted that such instability is not confined to IDUs. All users of mood-altering substances, both illicit and licit (including alcohol) can experience periods of lifestyle instability. Likewise, non-drug users with behavioural problems, such as borderline and antisocial personality disorders, and those with serious mental illness, may also encounter such instability. Lifestyle instability can further complicate treatment adherence issues in resource-poor settings. Consequently, the underlying health and psychosocial reasons for lifestyle instability should receive as much attention as the provision of ART.

The issues that have to be addressed in trying to improve stability include patterns of drug use, the level of drug dependence, and

emotional, legal, living and income circumstances. These issues are often multiple and complex, and dealing with them may require significant amounts of time and resources. It is therefore desirable to tackle them as soon as is practicable, preferably before the commencement of ART.

Opioid agonist pharmacotherapies, such as methadone maintenance treatment, have proved effective in the management of opioid dependence, improving overall health and psychosocial stability among IDUs [185-187]. Similar drug replacement approaches to the management of psychostimulant dependence have also produced encouraging results[145, 188]. Furthermore, such programmes have the advantage of allowing direct observation of the concomitant administration of ART. This helps to assure adherence to treatment while enabling timely management of other potentially significant clinical problems, such as drug interactions, should they arise.

It is therefore recommended that, where feasible, countries promote and support the development of integrated programmes involving the direct observation of therapies for the management of both drug dependence and HIV infection among IDUs. However, access to ARVs and other HIV treatments for IDUs should be based on clinical considerations only; the non-participation of IDUs in drug treatment programmes should not in itself justify exclusion from ART.

2. HIV treatment dosage regimens

Progress towards the development of single daily dosage regimens is being made in the ARV field and their standardization will be of advantage to all HIV-infected populations. Physicians in many countries currently prescribe a once-daily combination of ddI/3TC with EFZ or NVP to IDU clients for whom there are significant ongoing problems of adherence to treatment. Further studies on this matter are, however, required. EFZ should be avoided among female IDUs of childbearing age who may become pregnant and in IDUs with severe psychiatric comorbidity. This should be balanced against the risk of hepatotoxicity associated with NVP. This may be greater among patients with chronic hepatitis B and/or C infections, which are highly prevalent among IDUs. These issues should be taken into consideration by programme planners.

B. Potential drug interactions and side-effects associated with injecting drug use

It is important to minimize any drug interactions and side-effects of HIV treatments. The occurrence of complications of treatment may lead to its premature cessation, particularly if clients are at all ambivalent about receiving it (Chapter XV, Table 10, Annexes 8 and 11).

There are numerous potential drug interactions between ARV medications and methadone and other opioids. Of particular concern are decreases in blood methadone levels which might trigger opioid withdrawal symptoms (i.e. under coadministration of ABC, NVP, EFV, RTV, and NFV); adaptations of the methadone dose may be necessary in this circumstance. The coadministration of ARVs and methadone might also lead to clinically significant increases in ARV (i.e. ZDV) blood levels or reduce the bioavailability of ARVs, as has been observed with ddI; again, it may be necessary to modify dosages. The monitoring of therapeutic drug levels is still an area of investigation and is not a consideration for resource-limited settings.

Buprenorphine is increasingly being used as a replacement maintenance therapy for opioid dependence in some countries. However, little is known or documented about its interactions with HIV treatments, so close monitoring is recommended until further information is available.

Rifampicin, often prescribed in the management of TB, induces hepatic enzymes leading to opioid withdrawal, especially among IDUs receiving daily methadone in maintenance programmes. Such patients need an increased dose of methadone, commenced beforehand and maintained for as long as they are also receiving rifampicin and up to a month after its cessation.

It is also important to be aware of the significant analgesic properties of opioids, which can mask early symptoms of serious side-effects of HIV medications such as peripheral neuropathy and pancreatitis. All symptoms reported by IDUs which suggest such side-effects should be carefully evaluated.

C. Public health implications

In all country settings it is important that IDUs with HIV infection have access to the means to prevent the further transmission of

HIV to sexual partners and other IDU cohorts. It should also be recognized that, in many settings, IDUs engage in commercial sex work, thus increasing the need to emphasize the risk of sexual transmission of HIV. Settings where IDUs have access to HIV treatments should be assessed for their appropriateness to provide sterile injecting equipment and condoms and other means of minimizing the transmission of HIV infection.

XIV. DRUG ADHERENCE

ARV drug adherence is well recognized to be one of the key determinants of the success of therapy [13]. Poor adherence can lead to virological failure, the evolution of drug resistance and subsequent immunological and clinical failure [90, 189-209]. Adherence is promoted by simplified, well-tolerated regimens involving as few pills as possible administered no more than two times a day. It is important to counsel patients carefully in advance of initiating therapy; this typically involves a coordinated effort by physicians, nurses and other health care providers. ART should not be started at the first clinic visit. It is important to have a period of education and preparation aimed at maximizing adherence. Once treatment has begun, continued monitoring of adherence is essential. In the developed world it has been difficult to define a simple effective method of adherence monitoring for all settings. Assessment by physicians has repeatedly proved to be the least reliable approach. Pill counts are quantitatively useful but are subject to error and manipulation. Validated patient questionnaires have proved one of the more reliable, easily instituted tools for monitoring adherence in the outpatient setting [210, 211].

No single tool, however, can be applicable in all regions and cultures, so each country and/or centre should develop a brief, culturally appropriate patient questionnaire for assessing and monitoring adherence. In some settings, sites may wish to try to introduce directly observed therapy (DOT) with carers' or family members' assistance. In particular, sites with tuberculosis treatment programmes may wish to consider this, although the open-ended nature of ART, as opposed to the limited course of treatment for tuberculosis, raises questions about the sustainability of such an approach. Innovative models such as the use of DOT during an initial training period for patients should be evaluated. However, ongoing attention to and reinforcement of adherence throughout the entire course of ART comprise an essential part of any successful treatment programme and should be built into country-specific programmes.

XV. MONITORING ANTIRETROVIRAL THERAPY

The baseline evaluation and continuing monitoring of ART are important for assessing the effectiveness of this intervention and ensuring safety. In resource-limited settings, decisions about the minimal standard necessary have to be made. For all patients aged 18 months and older it is assumed that HIV infection is documented on the basis of a positive HIV antibody test (see Chapter XI for considerations relating to children under 18 months of age).

A. Clinical monitoring

1. Baseline clinical assessment

The baseline medical history should include essential demographic characteristics, the past medical history including major illnesses (e.g. tuberculosis), hospitalizations and surgeries, the length of time since the diagnosis of HIV infection, and current medications and symptoms. In the case of women, current or planned pregnancy and the access to contraceptive services should be reviewed.

The baseline physical examination should include vital signs, weight and details of any abnormalities of the eyes (including fundi if possible), oropharynx, lymph nodes, lungs, heart, abdomen, extremities, nervous system and genital tract.

The preparation of the patient for ART should include a review of the expected benefits and potential side-effects of the regimen chosen, a review of possible drug interactions (e.g. with oral contraceptives), the concept of partnership between patient and carer, the probability of lifelong commitment to treatment, the critical need to maintain safe sexual practices in order to prevent HIV transmission, the importance of drug adherence for a successful outcome, and the need to report any perceived side-effects of the medications. In some cases the latter may be life-saving, e.g. in respect of symptoms related to ABC hypersensitivity or NVP-associated hepatotoxicity.

Once ART has commenced a reasonable schedule for clinical monitoring includes a first follow-up visit one month after initiation (which may also be useful for evaluating and possibly reinforcing adherence to antiretroviral treatment) and at least one visit every

three to four months thereafter. Monthly visits, which can be combined with drug dispensing, are encouraged as they are useful opportunities to reinforce adherence. At each visit, enquiries should be made regarding any new symptoms that may be related to drug side-effects, HIV disease progression or intercurrent processes.

2. Clinical monitoring for toxicities and effectiveness of antiretroviral drugs/regimens

Patients should be informed about the symptoms of ARV drug toxicities and should be aware of the need to seek care and/or to stop therapy in the interim if necessary. A detailed description of the different syndromes and drug-specific adverse effects linked to individual antiretroviral drugs is given below and in Table 10 and Annex 11.

Whether CD4 cell monitoring is available or not, the clinical evaluation of the effectiveness of ART is important and helpful. The basic parameters examined should include: the patient's perception of how he/she is faring on treatment; changes in body weight over the course of therapy; changes in the frequency and/or severity of HIV-associated symptoms (e.g. fevers, diarrhoea) and physical findings (e.g. oropharyngeal or vulvovaginal candidiasis); and signs of immune reconstitution syndromes or HIV-related disease progression.

B. Laboratory monitoring

1. Basic laboratory monitoring for toxicity and effectiveness of antiretroviral therapy

Certain laboratory investigations are recommended as the basic level of care that is necessary in order to be able to embark safely on ART. They should either be available on site or by the transportation of specimens to a local reference laboratory, in which case the results should be rapidly returned to the requesting clinician. Such tests are needed in order to identify potential toxic reactions and then to trigger changes in drug regimes in accordance with local protocols; or they are required as adjuncts to monitoring the effectiveness of ART. The tests should be performed at baseline, before the initiation of ART, and at follow-up as indicated. The absolute minimum of laboratory tests to be performed before initiating ART are an HIV antibody test (in persons aged 18 months or more) and a haemoglobin or haematocrit determination. Basic testing should also include a white blood cell count and differential (to permit assessment of neutropenic side-effects

and the total lymphocyte count), determinations of the serum alanine or aspartate aminotransferase level in order to assess the possibility of hepatitis coinfection and to monitor for hepatotoxicity, of serum creatinine and/or blood urea nitrogen in order to assess baseline renal function, and of serum glucose in order to allow for the propensity of PIs to induce insulin resistance, and pregnancy tests for women. Increases in total lymphocyte counts are a reasonable though imprecise reflection of the immune response to ART.

If resources permit, additional baseline and routine laboratory monitoring can include the determination of serum bilirubin, amylase and lipids (triglycerides and cholesterol). WHO recommends that these tests be available in facilities at the district level. Other tests may be indicated if drug toxicity or clinical disease progression is suspected.

2. CD4+ lymphocyte counts

CD4+ lymphocyte counts, or percentages in children, are one of the most useful and reliable ways of assessing whether an HIV-positive patient should start ART. They are, of course, also extremely important in the assessment of the effectiveness of ART: increases of over 100 CD4 cells/mm^3 in the first 6-12 months are typically seen in an ARV-naïve, adherent patient with drug-susceptible virus. Higher elevations can be seen and the response often continues during subsequent years in individuals who are maximally virologically suppressed. Immunological failure on therapy can also be assessed. In adults, a useful definition of imunological failure is a return to the pre-therapy baseline or a fall of more than 30% from the peak [16].

The current technology for measuring CD4 counts is too costly to perform and requires flow cytometry. These factors severely limit the number of laboratories that can perform counts in resource-constrained settings. One of the most crucial needs in the developing world is universal access to affordable and locally usable CD4 testing technology. This is an urgent priority that should be pursued in parallel with the planned massive scale-up of ART. WHO recommends that simple low-cost CD4 technologies be available at central and provincial levels in resource-limited settings.

3. Plasma HIV RNA levels (viral load)

When already available in specific settings, or whenever it becomes less expensive and less technically demanding, the level of plasma

HIV-1 RNA is clearly a useful indicator of the activity of an ARV regimen in individual patients. Because of its high cost and poor availability in resource-constrained settings, however, it is not recommended as an assessment tool for managing ARV treatment in the present guidelines. The lack of availability of viral load monitoring implies that treatment failure has to be assessed immunologically and clinically rather than virologically. The implications of this have been discussed above. As with CD4, inexpensive and implementable methods for viral quantitation in plasma or serum are urgently needed. They can be expected to improve the effectiveness of ARV programmes and the care of individual patients. In the near term, viral load testing and viral resistance assays, where available, would probably be limited to the central level of the health system.

C. Antiretroviral drug toxicity

While HAART has led to substantial reductions in morbidity and mortality in industrialized countries, toxicity is not uncommon. In the Swiss HIV Cohort Study, 45% of patients on potent ART had clinical adverse events and 27% had laboratory adverse events that were considered to be probably or definitely attributable to therapy; however, only 9% of clinical and 16% of laboratory adverse events were serious or severe [212]. The use of drugs with similar toxicities should be avoided if possible. Toxicity can affect adherence to potent ART and can thus affect the overall efficacy of treatment. Patients should be counselled about the potential side-effects of the drugs they receive before starting therapy in order to enhance adherence and the early identification of serious toxicities. Some toxicities are transient and diminish with continued treatment, while others are potentially life-threatening and require discontinuation of the drug concerned.

Drugs of the NNRTI and PI classes (particularly RTV, even at low doses) interact with the cytochrome P450 enzyme system, resulting either in the inhibition or induction of these enzymes. When coadministered with other drugs that are metabolized by the cytochrome P450 system, increases or decreases in the given NNRTI or PI and/or of the concomitant medication may occur. This can result in the potential for increased toxicity because of elevated drug concentrations (or increased efficacy, as in RTV-boosted PI regimens) or drug failure attributable to subtherapeutic drug concentrations. The health care provider should carefully review concomitant medications and the requirements for dose modification if necessary (Annex 8).

Some toxicities are class-specific, overlapping between all drugs in a class, while other toxicities are drug-specific. Class-specific toxicity is reviewed below and within-class drug-specific toxicities are briefly discussed. Table 10 and Annex 11 indicate the monitoring and management of common drug toxicities.

1. Nucleoside analogue reverse transcriptase inhibitors

Unusual but serious toxicities that can occur in patients receiving NsRTIs include lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy and peripheral neuropathy. Although some toxicities have been reported with all NsRTIs (e.g. lactic acidosis), others (e.g. bone marrow suppression associated with ZDV; peripheral neuropathy with d4T and ddI; pancreatitis with ddI and 3TC) may predominantly occur with specific NsRTIs.

a. Class-specific: lactic acidosis/hepatic toxicity

Asymptomatic low-level hyperlactataemia has been reported in 21% of NsRTI-treated patients but is not predictive of lactic acidosis; symptomatic hyperlactataemia is less common and severe lactic acidosis and hepatic steatosis develop in only a minority of patients [213, 214]. Although uncommon, lactic acidosis is associated with a high fatality rate (33-57%). Risk factors include the female gender, a high body mass index, prolonged NsRTI use, and, possibly, pregnancy, acquired riboflavin and thiamine deficiency, and d4T use [213, 214]. The initial symptoms are variable; a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnoea and dyspnoea) or neurological symptoms (including motor weakness). Laboratory abnormalities can include hyperlactataemia, increased anion gap, and elevated aminotransferases, creatine phosphokinase, lactate dehydrogenase, lipase and amylase. Microvesicular steatosis is seen on histological examination of the liver. Cases have occurred as early as one month and as late as 20 months after the commencement of therapy [213]. ART should be discontinued in patients with these symptoms, because otherwise there may be progressive toxicity with severe lactic acidosis and respiratory failure. Symptoms associated with lactic acidosis may continue or worsen following the discontinuation of ART. Therapy is primarily supportive (fluid, bicarbonate administration and respiratory support), although in uncontrolled cases the administration of riboflavin and/or thiamine has been described as beneficial. After

the resolution of symptoms, regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either ABC or TDF. Other NsRTIs (ZDV, ddI, 3TC, d4T) should not be used following an episode of symptomatic lactic acidosis. The routine monitoring of serum lactate levels in asymptomatic patients is not recommended as part of routine clinical practice.

Liver toxicity, manifested as symptomless increases in liver transaminases, with normal bilirubin, occurs in 5-15% of patients receiving NsRTIs. Hepatitis is more uncommon, occurring in fewer than 1%, and has been reported with all NsRTIs except 3TC and ABC [215]. NsRTI-associated liver toxicity with hepatic steatosis is not usually seen until after more than six months of therapy.

b. Abacavir: hypersensitivity syndrome

Approximately 3-5% of adults and children receiving ABC develop a potentially fatal hypersensitivity reaction [216]. Findings suggestive of this diagnosis include: involvement of multiple organ systems, resulting in a constellation of symptoms; acute onset with worsening of the symptoms after each dose of ABC; occurrence in the first few weeks after initiating ABC (although these reactions may occur at any time during therapy) [217]. Symptoms include fever, gastrointestinal complaints (nausea, vomiting, diarrhoea or abdominal pain), malaise, fatigue, and/or respiratory symptoms (pharyngitis, cough or dyspnoea). Although these symptoms overlap with those of common infectious illness, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction than of illnesses such as influenza or rotaviral disease, which usually involve symptoms in only one organ system. Other symptoms include arthralgia, myalgia, headache, oedema and paraesthesia. Physical findings may include lymphadenopathy, ulceration of mucus membranes, and maculopapular or urticarial skin rash. The rash is often clinically unimpressive, and only occurs in about 70% of cases; fever may also be absent, although 98% of cases have either fever and/or rash [217]. Laboratory abnormalities can include elevated liver enzymes, creatine phosphokinase, creatinine and thrombocytopenia. Over 93% of hypersensitivity reactions occur during the first six weeks of treatment, with a median of 8 days from the start of therapy to the onset of the reaction. Patients experiencing this constellation of symptoms should be advised to seek medical care as soon as possible, and ABC should be stopped immediately if the health care provider suspects a hypersensitivity reaction. Therapy is supportive, e.g.

intravenous hydration. The reaction usually subsides following drug discontinuation, although symptoms may continue to worsen for one or two days after this. ABC should never be restarted because hypotension, renal and respiratory insufficiency, and death have occurred within hours of rechallenge. Genetic susceptibility to ABC hypersensitivity has been described in a cohort from Australia, with an increased likelihood of this reaction in individuals with HLA-B5701, HLA-DR7 and HLA-DQ3 alleles [218]. Further research is needed in order to evaluate potential genetic linkage to ABC hypersensitivity in racially diverse populations, particularly those in resource-poor countries.

c. Didanosine

The most common symptoms associated with ddI are diarrhoea, nausea, vomiting and/or abdominal pain, with an incidence of 5-18% [219]. The most serious side-effects are peripheral neuropathy and pancreatitis. Peripheral neuropathy has been reported in 6-15% of patients receiving currently recommended doses; the risk may be higher in patients treated with other neurotoxic drugs, including d4T. The symptoms include pain, tingling or numbness in the hands or feet. Distal sensory loss, mild muscle weakness, and areflexia may also occur. The symptoms usually resolve within 2-3 weeks after drug discontinuation. Pancreatitis has been reported in 1-7% of patients treated with currently recommended ddI doses; fatal pancreatitis is reported in about 1% of ddI-treated patients. The clinical symptoms include nausea, vomiting and abdominal pain, with elevated serum pancreatic amylase or lipase. The incidence is dose-related and is increased in patients with a prior history of pancreatitis, alcohol abuse, morbid obesity, hypertriglyceridaemia, gallstones, or receipt of other medications known to cause pancreatitis (e.g. pentamidine). Didanosine should be suspended in patients with suspected clinical pancreatitis and permanently stopped in those with confirmed pancreatitis. Mild asymptomatic elevations in pancreatic enzymes, however, can often be managed without discontinuation of the drug.

d. Lamivudine

Lamivudine is generally well tolerated. Headache, fatigue and gastrointestinal upset have been reported. The major serious reported toxicities are pancreatitis, primarily in children with advanced disease who are receiving treatment, and peripheral neuropathy. Rarely, neutropenia and hepatic toxicity have been reported.

e. Stavudine

The primary toxicity associated with d4T therapy is peripheral neuropathy, which is dependent on both the dose and the duration of treatment and is more common in patients with advanced HIV disease and those who are being treated with other neurotoxic drugs, including ddI [220]. The symptoms usually resolve within 2-3 weeks after the discontinuation of d4T. Compared to treatment with other NsRTIs, treatment with d4T may be associated with more frequent occurrences of elevated liver transaminases/hepatitis, lipodystrophy syndrome, pancreatitis (particularly if d4T is administered with ddI or hydroxyurea), and lactic acidosis [69, 213, 221]. Rare occurrences of ascending neuromuscular weakness, including respiratory failure and death, resembling Guillain-Barre syndrome, have been reported in patients receiving d4T; most cases have had concomitant lactic acidosis or hyperlactataemia. If motor weakness develops in a patient receiving d4T the drug should be stopped, and permanent discontinuation of d4T should be considered in cases of confirmed lactic acidosis.

f. Zidovudine

The most common toxicities associated with ZDV are haematological: severe macrocytic anaemia and/or granulocytopenia occur in over 5-10% of patients. Haematological toxicity is dose-related and is more common in patients with advanced HIV disease and in those receiving concomitant bone marrow suppressive medications, such as ganciclovir, pyrimethamine or hydroxyurea. Supportive treatment (including transfusion) or temporary lowering of the ZDV dose should be tried before the drug is discontinued. Erythropoietin support is not an option in the developing world because of its high cost. ZDV has also been associated with reversible myopathy in about 17% of patients [215], with symptoms of myalgia, proximal weakness, wasting accompanied by increased creatinine phosphokinase, and cardiomyopathy. Fatigue, headache and nausea occur in 5-10% of patients but are often transient despite continued therapy; abnormal nail pigmentation has been reported.

2. Non-nucleoside reverse transcriptase inhibitors

a. Class-specific: rash and hepatitis

Serious toxicities reported with all the NNRTIs include rash and hepatotoxicity. However, a hypersensitivity syndrome with rash,

including Stevens-Johnson syndrome, has only been described for NVP, and there does not appear to be cross-reactivity for rash between EFZ and NVP. EFZ may therefore be considered as a substitute for NVP if moderate rash occurs without mucosal involvement or systemic symptoms. Most clinicians would not, however, use another NNRTI in a patient who has had a severe cutaneous reaction to NVP, but would rather use a regimen including other drug classes. Hepatitis, which on rare occasions is fatal, has been reported with all NNRTIs. An analysis of data from several AIDS Clinical Trials Group studies found no difference in the rate of grade 3 or 4 transaminase elevation in individuals receiving NVP or EFZ, but other studies have suggested that rates may be higher with NVP [222]. The lack of rash cross-reactivity between NVP and EFZ suggests that, if severe hepatic toxicity occurs during NVP therapy, the risk of hepatotoxicity with EFZ may be no higher than background rates with the drug.

b. Efavirenz: central nervous system effects and teratogenicity

Adverse effects on the central nervous system have been reported in 30-50% of patients treated with EFZ, with reported symptoms of altered sensorium including dizziness, headache, insomnia, depression, impaired concentration, agitation, disturbing dreams/ nightmares, and somnolence. Under 2% of patients receiving EFZ may experience serious psychiatric symptoms, including severe depression, delusion, manic episodes or suicidal ideation, predominantly in persons with a history of mental illness or substance abuse. Patients who receive EFZ should be aware that such effects may occur. The administration of EFZ at bedtime during the first two to four weeks of therapy or in patients who have persistent adverse symptoms affecting the CNS can improve tolerance of the effects. Splitting the dose does not reduce the incidence or severity of this side-effect. EFZ has been associated with significant congenital abnormalities of the CNS in primates exposed to EFZ in utero at drug exposures similar to human exposure, and there has been a report of myelomeningocele in a human infant exposed to EFZ in utero. Pregnancy should be avoided in women receiving EFZ and its use should be avoided particularly during the first trimester (see Chaper X).

c. Nevirapine: severe rash and hepatitis

The primary NVP toxicities of clinical concern are skin rash and hepatic toxicity. NVP-associated rash develops in some 17% of patients, with serious, i.e. grade 3 or 4, rash requiring treatment

discontinuation in about 6-8% [223]. Rash usually occurs during the first two to four weeks of treatment; only unusually does it first occur after eight weeks of therapy. Some limited data suggest that rash may be more frequent in women or persons of Asian descent [224-226]. The rash is usually erythematous, maculopapular, confluent and most prominent on the body and arms, it may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis has been reported in about 0.3% of infected individuals receiving NVP. A hypersensitivity syndrome, consisting of systemic symptoms of fever, myalgia, arthralgia, hepatitis and eosinophilia can precede the rash or can occur without rash. If the rash is mild or moderate (erythema or maculopapular rash with or without pruritis or dry desquamation without constitutional symptoms or mucosal lesions), NVP can be continued cautiously while the rash is observed or EFZ can be substituted for NVP. If mild to moderate rash occurs during the two-week, half-dose lead-in period of NVP therapy, the drugs should be stopped until the rash resolves and should be cautiously restarted as from the beginning of the lead-in phase. NVP should be permanently discontinued in patients who have severe rash, development of cutaneous bullae or target lesions, or mucosal involvement or symptoms consistent with hypersensitivity. Such patients may experience a more rapid onset of rash, a potential increase in its severity or even a fatal reaction if rechallenged with drug. In patients with severe reactions the NNRTI class of drugs should be avoided. Reactions may worsen temporarily after drug discontinuation. The use of steroids does not prevent NVP hypersensitivity [215].

Hepatotoxicity can occur in the absence of rash or the hypersensitivity syndrome. The reported incidence of increased serum transaminase levels in patients receiving chronic NVP therapy is about 13-17%; severe hepatitis has been reported in 1-9% of patients [227-230]. While most hepatic toxicities occur within the first 12 weeks after the start of therapy, one-third of cases first occur after NVP therapy has been in progress for 12 weeks or more. Symptoms of hepatitis can be non-specific, and include fatigue, malaise, anorexia, nausea and jaundice. Hepatitis may be associated with a hypersensitivity reaction involving drug rash, eosinophilia and systemic symptoms [231]. Rarely, hepatotoxicity can result in hepatic failure and death. An increased risk of NVP hepatotoxicity has been reported in patients with baseline elevations in serum transaminases or a history of alcohol abuse, and in older patients, females, and patients affected by coinfection with hepatitis B or C or having an elevated CD4 count, suggesting an immunological component to the toxicity [227-230, 232]. NVP should be permanently discontinued in patients with NVP-associated hepatitis.

3. Protease inhibitors

Infrequent but serious toxicities that can occur in patients receiving any of the PIs include insulin resistance, diabetes, hyperlipidaemia, lipodystrophy, increased bleeding episodes in haemophiliacs, hepatitis and bone disorders, although certain PIs may be associated with a higher incidence of some of these events than occurs with others (e.g. RTV and hyperlipidaemia) [233]. Other toxicities are specific to the particular PI used, such as nephrolithiasis with IDV.

a. Class-specific: insulin resistance/diabetes

Insulin resistance occurs in up to 40% of patients treated with PIs, and hyperglycaemia, new-onset diabetes mellitus, diabetic ketoacidosis, and exacerbations of pre-existing diabetes mellitus have also been reported [234, 235]. Hyperglycaemia has been reported in 3-17% of patients receiving PIs; the median onset time is 60 days after the initiation of therapy, ranging from 2 to 390 days; about 1% of these patients develop clinical evidence of diabetes. Patients receiving PIs should be advised about the warning signs of hyperglycaemia, such as polydipsia, polyuria and polyphagia. Hyperglycaemia resolves in some but not all patients after the discontinuation of therapy. Most experts, however, would continue HAART with supportive therapy (oral hypoglycaemic drugs or insulin) in the absence of severe diabetes.

b. Class-specific: hyperlipidaemia

Elevated triglycerides and/or cholesterol have been linked to treatment with all the PIs, although the increases tend to be higher in patients receiving RTV [235]. The association of these findings with the potential for increased risk of events linked to hyperlipidaemia in patients without HIV infection, such as cardiovascular disease or pancreatitis, is unclear. Most experts continue PI therapy in patients with mild to moderately severe lipid elevations (e.g. triglycerides below 750-1000 mg/dl or LDL cholesterol below 160 mg/dl. Some patients have experienced resolution of lipid abnormalities following the discontinuation of PIs and a switch to an NNRTI or NsRTI-based potent ART regimen [236].

c. Class-specific: lipodystrophy

Changes in body fat distribution (lipodystrophy) have been reported in as many as 80% of patients receiving PIs. They have also been

described in connection with NsRTI therapy (particularly d4T-containing regimens) [69, 237, 238]. These changes are gradual and generally not apparent until months after the initiation of therapy. Clinical findings include: central obesity, peripheral fat wasting and lipomas; visceral fat accumulation; dorsocervical fat accumulation ('buffalo hump"); extremity wasting with venous prominence; facial thinning; and breast enlargement. Central fat accumulation appears to be more associated with PIs and peripheral fat wasting with NsRTIs, although this has not been definitively established. Hyperlipidaemia and insulin resistance are frequently but not always associated with lipodystrophy. Therapeutic strategies have included switching classes of antiretroviral drugs and exercise training. The reversal of body shape changes may not occur or may do so only slowly after discontinuation of the offending antiretroviral agent or agents. Specific drug treatments for this condition are under active investigation.

d. Class-specific: increased bleeding episodes in haemophiliacs

Increased spontaneous bleeding episodes have been reported in patients with haemophilia A or B who are receiving PIs, including skin haematomas and haemarthrosis; more serious bleeding involving the gastrointestinal tract or intracranial sites has rarely been reported. The median time at which the onset of bleeding episodes occurred was 22 days after the initiation of PI therapy. Some patients have been able to continue therapy while receiving additional treatment with coagulation factor

e. Class-specific: hepatitis

PIs can cause hepatitis by an unknown mechanism. Severe hepatotoxicity is reported with increased frequency in patients receiving RTV-containing regimens. PI-associated elevation of liver transaminases can occur at any time during treatment; the risk factors include hepatitis B or C coinfection, alcohol, baseline elevated liver enzymes, the use of hepatotoxic agents and the use of d4T [239, 240].

f. Class-specific: bone disorders

Osteopenia, osteoporosis and avascular necrosis, usually of the femoral or humeral head, have been reported in adults and children receiving PI-containing HAART [241-243]. The association of these findings with potent ART has not been definitively established, although the risk appears higher in patients receiving PIs than in those on regimens that do not contain PIs.

g. Indinavir: nephrolithiasis/indirect hyperbilirubinaemia

The most serious side-effect of IDV in adults and children is nephrolithiasis, seen in about 9% of patients; it may be more frequent in children (13% developed haematuria according to one report), probably because of the difficulty in maintaining adequate hydration in this population [244]. Transient abnormal renal function, including acute renal failure, and interstitial nephritis have been observed in some patients with nephrolithiasis. If there are signs or symptoms such as flank pain with or without haematuria, the interruption of therapy for 1-3 days during the acute episode should be considered. Recurrence after IDV has been restarted occurs in only 50% of patients [215]. Adequate hydration is essential with IDV therapy; patients should be advised to consume at least 1.5 litres of water daily and more in hot weather [215]. Asymptomatic indirect hyperbilirubinaemia has been seen in about 10% of patients receiving IDV; in most cases the maximum bilirubin elevation was observed after one or more weeks of treatment; clinical adverse events such as jaundice and elevations in serum transaminases have been reported only rarely. IDV is unique among the PIs in being associated with retinoid-like side-effects, including alopecia, dry skin, dry lips and ingrown nails. About 3% of patients receiving IDV may develop oesophageal reflux.

h. Lopinavir/ritonavir

The most common side-effects of LPV/r are diarrhoea, asthenia, and triglyceride and cholesterol elevations (the latter may be attributable to the RTV component of the combination). Pancreatitis has been reported in adults, possibly secondary to high triglyceride levels, a risk factor for pancreatitis.

i. Nelfinavir

NFV is relatively well tolerated. The most common adverse effects include diarrhoea, abdominal pain, flatulence and rash. Patients should be warned that diarrhoea is most common at the start of therapy and usually, but not always, resolves on its own within a few days or weeks.

j. Saquinavir

SQV is well tolerated. The primary toxicity involves mild gastrointestinal disturbances such as nausea, diarrhoea and abdominal pain, and headache and reversible elevations in liver

transaminases. Nausea and diarrhoea are more common with the soft-gel formulation than with the hard-gel formulation.

Adverse effect	Possible offending drug(s)
Acute hepatitis	Nevirapine (NVP); efavirenz (EFZ) less common; more uncommon with zidovudine (ZDV), didanosine (ddI), stavudine (d4T) (<1%); and protease inhibitors, most frequently with ritonavir (RTV)
Acute pancreatitis	ddI, d4T; lamivudine (3TC) (infrequent)
Lactic acidosis	All nucleoside analogue reverse transcriptase inhibitors (NsRTIs)
Hyper-sensitivity reaction	Abacavir (ABC), nevirapine (NVP)

Table 10. Clinical signs and symptoms and the monitoring and management of symptoms of serious adverse effects of antiretroviral drugs which require drug discontinuation.

Clinical signs/symptoms	**Management**
Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia).	If possible, monitor serum transaminases, bilirubin. All ART should be stopped until symptoms resolve. NVP should be permanently discontinued.
Nausea, vomiting and abdominal pain.	If possible, monitor serum pancreatic amylase, lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NsRTI, preferably one without pancreatic toxicity (e.g. ZDV, ABC).
Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnoea and dyspnoea) or neurological symptoms (including motor weakness).	Discontinue all ART; symptoms may continue or worsen after discontinuation of ART. Supportive therapy. Regimens that can be considered for restarting ART include a PI combined with an NNRTI and possibly either ABC or TDF.
ABC: Constellation of acute onset of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea (with or without rash). While these symptoms overlap those of common infectious illnesses, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash.	Discontinue all ART until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with a change to different NsRTI if ABC-associated or to PI- or NsRTI based regimen if NVP-associated.

Adverse effect	Possible offending drug(s)
Severe rash / Stevens-Johnson syndrome	Non nucleoside reverse transcriptase inhibitors (NNRTIs): nevirapine (NVP), efavirenz (EFV)
Severe peripheral neuropathy	ddI, d4T, 3TC

Clinical signs/symptoms	Management
Rash usually occurs during the first two to four weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis has been reported in ~0.3% of infected individuals receiving NVP.	Discontinue all ARVs until symptoms resolve. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or Stevens-Johnson syndrome or toxic epidermal necrolysis; once resolves, switch ART regimen to different ARV class (e.g. three NsRTIs or two NsRTIs and PI). If rash is moderate (not severe) and without mucosal or systemic symptoms, change in NNRTI (e.g. NVP to EFV) could be considered after rash resolves.
Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.	Stop suspect NsRTI and switch to different NsRTI that does not have neurotoxicity (e.g. ZDV, ABC). Symptoms usually resolve in two to three weeks.

ANNEX 1. WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN ADULTS AND ADOLESCENTS

Clinical stage I

1. Asymptomatic
2. Persistent generalized lymphadenopathy

Performance scale 1: asymptomatic, normal activity

Clinical stage II

3. Weight loss, <10% of body weight
4. Minor mucocutaneous manifestations (seborrheic 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 consant), >1 month
10. Oral candidiasis (thrush)
11. Oral hairy leukoplakia
12. Pulmonary tuberculosis within the past year
13. Severe bacterial infections (i.e. pneumonia, pyomyositis)

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

Clinical stage IV

14. HIV wasting syndrome, as defined by the Centers for Disease Control and Prevention[a]
15. Pneumocystis 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 nodes
20. Herpes simplex virus infection, mucocutaneous >1 month, or visceral any duration
21. Progressive multifocal leukoencephalopathy
22. Any disseminated endemic mycosis (i.e. histoplasmosis, coccidioidomycosis)
23. Candidiasis of the oesophagus, trachea, bronchi or lungs
24. Atypical mycobacteriosis, disseminated
25. Non-typhoid Salmonella septicaemia
26. Extrapulmonary tuberculosis
27. Lymphoma
28. Kaposi's sarcoma
29. HIV encephalopathy, as defined by the Centers for Disease Control and Prevention.[b]

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

Note: both definitive and presumptive diagnoses are acceptable.

[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 2. WHO STAGING SYSTEM FOR HIV INFECTION AND DISEASE IN CHILDREN

Clinical stage I

1. Asymptomatic
2. Generalized lymphadenopathy

Clinical stage II

3. Unexplained chronic diarrhoea
4. Severe persistent or recurrent candidiasis outside the neonatal period
5. Weight loss or failure to thrive
6. Persistent fever
7. Recurrent severe bacterial infections

Clinical stage III

8. AIDS-defining opportunistic infections
9. Severe failure to thrive
10. Progressive encephalopathy
11. Malignancy
12. Recurrent septicaemia or meningitis

ANNEX 3. CHARACTERISTICS OF NNRTI-BASED REGIMENS

NNRTI-based regimen	Potency[a]	Low pill burden	Cold storage needed	Predicted early resistance	Drug class spared[b]	Few drug interactions
ZDV/3TC/EFZ[c]	++++	+++	No	M184V +/or NNRTI	PI	++
d4T/3TC/EFZ[c]	++++	++	No	M184V +/or NNRTI	PI	++
d4T/ddI/EFZ[c]	++++	++	No	M184V +/or NNRTI	PI	++
ZDV/ddI/EFZ[c]	++++	++	No	NNRTI	PI	++
ZDV/3TC/NVP	++++	+++	No	NNRTI	PI	++
d4T/3TC/NVP	++++	++	No	M184V +/or NNRTI	PI	++
d4T/ddI/NVP	++++	++	No	M184V +/or NNRTI	PI	++
ZDV/ddI/NVP	++++	++	No	NNRTI	PI	++

[a] Key to table: ++++ = most favorable; + = least favorable or information very limited; - = contraindicated or risks may outweigh benefits.

[b] For consideration of alternative regimen in the setting of treatment failure.

[c] EFZ should not be used in pregnant women or women for whom effective contraception cannot be assured (see text).

ANNEX 4. CHARACTERISTICS OF TRIPLE NSRTI-BASED REGIMENS

Triple NsRTI regimen	Potency [a]	Low pill burden	Cold storage needed
ZDV/3TC/ABC	++++	++++	No
d4T/3TC/ABC	++++	+++	No
d4T/ddI/ABC	++++	+++	No
ZDV/ddI/ABC	++++	+++	No

[a] Key to table: ++++ = most favorable; + = least favorable or information very limited; - = contraindicated or risks may outweigh benefits.

[b] For consideration of alternative regimen in the setting of treatment failure.

Predicted early resistance profile	Drug class spared[b]	Few drug interactions
M184V	PI and NNRTI	++++
M184V	PI and NNRTI	++++
M184V +/or NAMs	PI and NNRTI	++++
M184V +/or NAMs	PI and NNRTI	++++

ANNEX 5. CHARACTERISTICS OF PI-BASED REGIMENS

PI-based regimen	Potency [a]	Low pill burden	Cold storage needed [b]	Predicted early resistance profile
ZDV/3TC/NFV	+++	++	No	M184V D30N or L90M
d4T/3TC/NFV	+++	++	No	M184V D30N or L90M
d4T/ddI/NFV	+++	++	No	NAMs[d] D30N or L90M
ZDV/ddI/NFV	+++	++	No	NAMs[d] D30N or L90M
ZDV/3TC/IDV/r	++++	++	Yes	M184V
d4T/3TC/IDV/r	++++	++	Yes	M184V
d4T/ddI/IDV/r	++++	++	Yes	NAMs[d]
ZDV/ddI/IDV/r	++++	++	Yes	NAMs[d]
ZDV/3TC/LPV/r	++++	++	Yes	M184V
d4T/3TC/LPV/r	++++	++	Yes	M184V
d4T/ddI/LPV/r	++++	++	Yes	NAMs[d]
ZDV/ddI/LPV/r	++++	++	Yes	NAMs[d]
ZDV/3TC/SQV/r[e]	++++	++	Yes	M184V
d4T/3TC/SQV/r[e]	++++	++	Yes	M184V
d4T/ddI/SQV/r[e]	++++	++	Yes	NAMs[d]
ZDV/ddI/SQV/r[e]	++++	++	Yes	NAMs[d]

Drug class spared[c]	Few drug interactions
NNRTI	++
NNRTI	++
NNRTI	++
NNRTI	++
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+
NNRTI	+

[a] Key to table: ++++ = most favorable; + = least favorable or information very limited; - = contraindicated or risks may outweigh benefits.

[b] For long-term storage of RTV component.

[c] For consideration of alternative regimen in the setting of treatment failure.

[d] Nucleoside analogue mutations.

[e] Hard-gel or soft-gel formulation of SQV may be used when combined with RTV.

ANNEX 6. CHARACTERISTICS OF NNRTI-, TRIPLE POPULATIONS

	Pregnant women	Children <3 years	Children ⩾3 years	Tuberculosis coinfected
NNRTI-based regimens				
ZDV/3TC/EFZ	-	-	++++	+++
d4T/3TC/EFZ	-	-	+++	+++
d4T/ddI/EFZ	-	-	+++	-
ZDV/ddI/EFZ	-	-	+++	+++
ZDV/3TC/NVP	++++	++++	++++	+
d4T/3TC/NVP	+++	+++	+++	+
d4T/ddI/NVP	-	+++	+++	-
ZDV/ddI/NVP	++++	+++	+++	+
Triple NsRTI-based regimens				
ZDV/3TC/ABC	++	+++	++++	++++
d4T/3TC/ABC	++	+++	++++	++++
d4T/ddI/ABC	-	++	+++	++
ZDV/ddI/ABC	++	++	+++	++
PI-based regimens				
ZDV/3TC/NFV	++++	++	+++	-
d4T/3TC/NFV	+++	++	+++	-
d4T/ddI/NFV	-	++	+++	-
ZDV/ddI/NFV	+++	++	+++	-
ZDV/3TC/IDV/r	++	-	+	-
d4T/3TC/IDV/r	++	-	+	-
d4T/ddI/IDV/r	-	-	+	-
ZDV/ddI/IDV/r	++	-	+	-
ZDV/3TC/LPV/r	+	++	+++	-
d4T/3TC/LPV/r	+	++	+++	-
d4T/ddI/LPV/r	-	++	+++	-
ZDV/ddI/LPV/r	+	++	+++	-
ZDV/3TC/SQV/r	++++	-	+	++
d4T/3TC/SQV/r	+++	-	+	++
d4T/ddI/SQV/r	-	-	+	-
ZDV/ddI/SQV/r	+++	-	+	+

[a] Key to table: ++++ = most favorable; + = least favorable or information very limited;
- = contraindicated or risks may outweigh benefits.

NSRTI- AND PI-BASED REGIMENS IN SPECIAL

Injecting drug users	Group O infected, HIV-2 infected
++	-
++	-
++	-
++	-
++	-
++	-
+	--
++	++++
++++	++++
++++	++++
++	++++
+++	++++
+++	++++
+++	++++
+++	++++
+++	++++
+++	++++
+++	++++
++	++++
++	++++
+++	++++
+++	++++
++	++++
++	++++
+++	++++
+++	++++
++	++++
++	++++

ANNEX 7. ANTIRETROVIRAL DOSAGE REGIMENS FOR ADULTS AND ADOLESCENTS

Drug class/drug	Dose
Nucleoside RTIs	
Zidovudine (ZDV)	300 mg twice daily
Stavudine (d4T)	40 mg twice daily (30 mg twice daily if <60 kg)
Lamivudine (3TC)	150 mg twice daily
Didanosine (ddI)	400 mg once daily (250 mg once daily if < 60 kg)
Abacavir (ABC)	300 mg twice daily
Nucleotide RTI	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside RTIs	
Efavirenz (EFZ)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, then 200 mg twice daily
Protease inhibitors	
Nelfinavir (NFV)	1250 mg twice daily
Indinavir/ritonavir (IDV/r)	800 mg/100 mg twice daily[b, c]
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily (533 mg/133 mg twice daily when combined with EFZ or NVP)
Saquinavir/ritonavir (SQV/r)	1000 mg/100 mg twice daily[c, d]

[a] 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 for renal or hepatic dysfunction or for potential drug interactions with other HIV and non-HIV medications.

[b] This dosage regimen is not approved but supportive data exist and the regimen is in common clinical use. Other IDV/r dosage regimens that range from 800 mg/200 mg twice daily to 400 mg/100 mg twice daily are also in clinical usage but more data are needed to determine the optimal dose combination.

[c] 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 twice daily when EFZ or NVP is used concomitantly. More drug interaction data are needed.

[d] This dosage regimen is not approved but supportive data exist for its use. Both the hard-gel and soft-gel capsule formulations can be used when SQV is combined with RTV.

ANNEX 8A. ANTIRETROVIRAL DRUG INTERACTIONS

Pharmacokinetic interactions occur when one drug alters the serum or tissue concentration of another by changing its absorption, distribution, metabolism or elimination. Such interactions can result in clinically significant changes in drug concentration which may require the dose of one or more drugs to be modified or may necessitate the use of an alternative drug or drugs. Annexes 8B and 8C list antiretroviral drug interactions that are of importance in resource-poor countries. Not all interactions are are listed, and the product insert information should be consulted. In comparison with the NNRTIs and PIs the NsRTIs have very limited drug interactions and they are therefore not included in the tables. Clinically significant pharmacokinetic interactions for the NsRTIs are primarily related to ddI buffer-associated decreases in the absorption of some drugs (see below).

Changes in drug absorption

Alteration of gastric pH

If a drug changes the gastric pH it can affect the absorption and hence the concentration of other drugs that have specific pH requirements for absorption. For example, ddI requires a higher gastric pH for optimal absorption; ddI is administered with an antacid buffer that raises the gastric pH. Thus, ddI decreases the absorption of drugs whose absorption requires low gastric pH, such as ketoconazole, itraconzole, tetracyclines, quinolone antibiotics, IDV and LPV/r. If coadministration occurs these drugs should be given two hours apart from ddI.

Presence or absence of food

Food can enhance or decrease the bioavailability of a drug, often bcause of its effect on gastric acidity. It is therefore recommended that some drugs, e.g. ddI and IDV, be administered one hour before or two hours after eating. Additionally, the bioavailablity of lipid-soluble drugs, such as efavirenz, may be enhanced when administered with a high-fat meal.

Chelation

The binding of two drugs/compounds to form insoluble complexes that cannot be absorbed can change the absorption of a drug. For example, the absorption of the fluoroquinolone drugs is significantly decreased by chelation with calcium in milk products or with cations such as those of aluminum, magnesium, iron or zinc found in antacids or multivitamins.

Changes in distribution

Protein-binding

Things that alter the protein-binding of a drug affect the amount of free drug that is available to produce a therapeutic effect. For example, warfarin is 99% protein-bound and if given with other protein-bound drugs, such as EFZ, it can be displaced from its protein sites. This places the patient at risk for bleeding and requires the prothrombin time to be monitored.

Hypoalbuminaemia

Patients with low albumin levels can experience an increased therapeutic effect and/or a risk for toxicity of drugs that are highly protein-bound, such as warfarin or phenytoin.

Changes in metabolism

Metabolism in the liver cytochrome P450 system

The induction or inhibition of various P450 enzymes by one drug can significantly alter the serum concentration of another drug that is metabolized by the same P450 enzyme. The PIs and NNRTIs are primarily metabolized by the P450 CYP3A4 isoenzyme and can inhibit or induce this isoenzyme, resulting in increases or decreases in the concentration of concomitantly administered drugs. Moreover, other drugs that inhibit or induce this isoenzyme can bring about increases or decreases in the concentration of concomitantly administered PIs and/or NNRTIs. Each PI and NNRTI has a different drug interaction profile, depending primarily on its potency as an inducer or inhibitor of the CYP3A4 and/or other P450 isoenzymes.

Of all the PIs, RTV is the most potent inhibitor of CYP3A4 and other isoenzymes, and consequently the largest amount of drug interactions and contraindications are associated with it. This property of RTV has been exploited through its use at low dose as a pharmacological booster with other PI drugs in order to raise their

serum concentration, thus allowing lower doses and/or decreased frequency of administration of the boosted PIs. IDV and NFV inhibit the CYP3A4 isoenzyme with similar potency. They are less potent inhibitors than RTV and present a smaller risk of drug interactions. SQV exhibits the smallest amount of drug interactions. NVP is a potent enzyme inducer, and EFZ is both an inducer and an inhibitor of CYP3A4. The many drug interactions associated with PIs and NNRTIs require that a careful review of medication be conducted before therapy is started, with attention to the potential need either to modify the drug dose or doses of the antiretroviral drug and/or the non-antiretroviral drug or to substitute an alternative drug.

Rifamycins have significant interactions with other drugs in relation to hepatic metabolism. Rifampicin is a potent inducer of hepatic metabolism and significantly decreases the concentration of PIs to subtherapeutic levels; the concomitant administration of PIs with rifampicin is not recommended, except possibly for SQV/r (see Chapter XII). Rifabutin is a less potent inducer of hepatic metabolism than rifampicin. However, rifabutin levels can be markedly increased with concomitant administration of some PIs, and this can result in an increased risk of, for example, myalgias, uveitis and neutropenia. The rifabutin dose may therefore have to be decreased if this drug is concomitantly administered with some PIs.

NFV, RTV and the NNRTIs can significantly decrease the estrogen concentration in oral contraceptives. Consequently, women taking these drugs cannot rely on oral contraceptives and should use another or an additional method of contraception. IDV and SQV do not affect estrogen levels unless RTV-boosting drugs are given (i.e. SQV/r). It is important to counsel women about the need for additional or alternative contraception if they are treated with these drugs.

PIs and EFZ can raise the serum concentration of cisapride and non-sedating antihistamines (astemizole, terfenadine), which can lead to cardiotoxicity. They can also increase the serum concentration benzodiazapines, and this can result in prolonged sedation. PIs and these other drugs should not, therefore, be administered concomitantly.

Changes in elimination

Kidney function

The inhibition of the tubular secretion of one drug by another that is eliminated by the kidney can result in changes in drug concentration. For example, probenecid can increase levels of ZDV.

ANNEX 8B. DRUG INTERACTIONS BETWEEN NON-NUC AND PROTEASE INHIBITORS

	Nevirapine (NVP)	**Efavirenz (EFZ)**	**Indinavir (IDV)**
Nevirapine	-	No effect on NVP EFZ AUC decreased 22% ***Recommendation:*** Standard dosing	NVP increased twofold IDV decreased 28% ***Recommendation:*** Change IDV dose to 1000 mg three times daily No change NVP
Efavirenz	-	-	No effect on EFZ IDV decreased 31% ***Recommendation:*** Change IDV dose to 1000 mg three times daily No change EFZ
Indinavir	-	-	-
Lopinavir	-	-	-
Nelfinavir	-	-	-

LEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
No effect on NVP LPV trough decreased 55% ***Recommendation:*** Consider LPV/r 533 mg/ 133 mg twice daily No change NVP	No effect on NVP NFV levels increased 10% ***Recommendation:*** Standard dosing	No effect on NVP SQV decreased 25% ***Recommendation:*** Standard dosing
No effect on EFZ LVP AUC decreased 40% ***Recommendation:*** Consider LPV/r 533 mg/ 133 mg twice daily No change EFZ	No effect on EFZ NFV increased 20% ***Recommendation:*** Standard dosing	EFZ decreased 12% SQV decreased 62% ***Recommendation:*** Do not coadminister (SQV/r boosting may be possible)
No effect on LPV IDV AUC and trough increased ***Recommendation:*** Change IDV dose to 600 mg twice daily No change LPV	NFV increased 80% IDV increased 50% ***Recommendation:*** Limited data for IDV 1200 mg twice daily with NFV 1250 mg twice daily	SQV increased fourfold to sevenfold ***No effect on IDV*** *Recommendation:* Insufficient data to provide recommendation
-	No data	SQV AUC/trough increased ***Recommendation:*** SQV 800 mg twice daily No change LPV/r
-	-	SQV increased twofold to fivefold NFV increased 20% ***Recommendation:*** Fortovase 1200 mg twice daily No change NFV

ANNEX 8C. DRUG INTERACTIONS INVOLVING INHIBITORS AND PROTEASE INHIBITORS OF REL

	Nevirapine (NVP)	**Efavirenz (EFZ)**	**Indinavir (IDV)**
Antifungal Ketoconazole	NVP increased 15-30% Ketoconazole decreased 63% ***Recommendation:*** Do not coadminister	No data	IDV increased 68% ***Recommendation:*** Change IDV to 600 mg three times daily
Antimycobacterials			
Rifampin	NVP decreased 37% ***Recommendation:*** Use with caution only if no alternatives available	EFZ decreased 25-33% ***Recommendation:*** Consider EFZ 800 mg daily	IDV decreased 89% ***Recommendation:*** Do not coadminister
Rifabutin	NVP decreased 16% ***Recommendation:*** Standard dosing	EFZ unchanged Rifabutin decreased 35% ***Recommendation:*** Increase rifabutin dose to 450-600 mg daily (or 600 mg two or three times weekly); EFZ no change	IDV decreased 32% Rifabutin increased twofold ***Recommendation:*** Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); IDV dose change to 1000 mg three times daily
Clarithromycin	NVP increased 26% Clarithromycin decreased 30% ***Recommendation:*** Standard dosing	EFZ unchanged Clarithromycin decreased 39% ***Recommendation:*** Do not coadminister	Clarithromycin increased 53% ***Recommendation:*** Standard dosing

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE EVANCE TO POOR COUNTRIES

Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
LPV decreased 13% Ketoconazole increased threefold ***Recommendation:*** None	No dose adjustment	SQV increased threefold ***Recommendation:*** Standard dosing
LPV AUCdecreased 75% ***Recommendation:*** Do not coadminister	NFV decreased 82% ***Recommendation:*** Do not coadminister	SQV decreased 84% when given without RTV ***Recommendation:*** If using SQV/RTV rifampin can be used at 600 mg/day or two or three times weekly
Rifabutin AUC increased threefold ***Recommendation:*** Decrease rifabutin dose to 150 mg daily; LPV/r no change	NFV decreased 32% Rifabutin increased twofold ***Recommendation:*** Decrease rifabutin dose to 150 mg daily (or 300 mg two or three times weekly); NFV dose increase to 1000 mg three times daily	SQV decreased 40% (RTV increases rifabutin levels fourfold) ***Recommendation:*** If using SQV/RTV, use rifabutin 150 mg two or three times weekly
No data	No data	Clarithromycin increased 45% SQV increased 177% ***Recommendation:*** Standard dosing

	Nevirapine (NVP)	**Efavirenz (EFZ)**	**Indinavir (IDV)**
Oral contraceptives	Estradiol decreased 20% ***Recommendation:*** Use alternative or additional methods	Estradiol increased 37%; no data on other components *Recommendation:* Use alternative or additional methods	When used with RTV: estradiol decreased *Recommendation:* Use alternative or additional methods
Methadone	Methadone decreased significantly ***Recommendation:*** Opioid withdrawal reported; may require increase in methadone dose	Methadone decreased significantly *Recommendation:* Opioid withdrawal reported; may require increase in methadone dose	No change but there may be a decrease if given with low-dose RTV ***Recommendation:*** When IDV is given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose
Anticonvulsant Phenobarbital	Unknown	Unknown	-
Lipid-lowering agents Simvastatin Lovastatin Atorvastatin Pravastatin	No data	No data	Potential for large increase in statin levels (except pravastatin) ***Recommendation:*** Do not coadminister except pravastatin; no dose adjustment

Lopinavir (LPV/r)	Nelfinavir (NFV)	Saquinavir (SQV)
Estradiol decreased 42% ***Recommendation:*** Use alternative or additional methods	Estradiol decreased 47%; norethindrone decreased 18% ***Recommendation:*** Use alternative or additional methods	When used with RTV: estradiol decreased ***Recommendation:*** Use alternative or additional methods
Methadone AUC decreased 53% ***Recommendation:*** Opioid withdrawal possible; may require increase in methadone dose	May decrease methadone levels ***Recommendation:*** Opioid withdrawal possible; may require increase in methadone dose	No data but may decrease if given with low-dose RTV ***Recommendation:*** When given with low-dose RTV: opioid withdrawal possible; may require increase in methadone dose
Unknown but may decrease LPV levels substantially ***Recommendation:*** Monitor anticonvulsant levels	Unknown but may decrease NFV levels substantially ***Recommendation:*** Monitor anticonvulsant levels	Unknown but may decrease SQV levels substantially ***Recommendation:*** Monitor anticonvulsant levels
Potential for large increase in statin levels ***Recommendation:*** Do not coadminister	Potential for large increase in statin levels ***Recommendation:*** Do not coadminister	Potential for large increase in statin levels ***Recommendation:*** Do not coadminister

	Nevirapine (NVP)	Efavirenz (EFZ)	Indinavir (IDV)
Additional drugs that should NOT be coadministered	***Herbs:*** St. John's wort, garlic supplements	***Antihistamine:*** astemizole, terfenadine ***Gastrointestinal:*** cisapride ***Psychotropic:*** midazolam, triazolam ***Ergot alkaloids:*** dihydroergotamine, ergotamine ***Herbs:*** St. John's wort, garlic supplements	***Antihistamine:*** astemizole, terfenadine ***Gastrointestinal:*** cisapride ***Psychotropic:*** midazolam, triazolam ***Ergot alkaloids:*** dihydroergotamine, ergotamine ***Herbs:*** St. John's wort, garlic supplements When IDV is used with low-dose RTV: ***Cardiac:*** flecainide, propafenone ***Neuroleptic:*** pimozide
Miscellaneous	Can induce glucosteroid metabolism, resulting in lower serum steroid levels	Monitor warfarin if used concomitantly	Grapefruit juice decreases IDV by 26%

Lopinavir (LPV/r)	**Nelfinavir (NFV)**	**Saquinavir (SQV)**
Antihistamine: astemizole, terfenadine Gastrointestinal: cisapride ***Psychotropic:*** midazolam, triazolam ***Ergot alkaloids:*** dihydroergotamine, ergotamine ***Herbs:*** St. John's wort, garlic supplements ***Cardiac:*** flecainide, propafenone ***Neuroleptic:*** pimozide	***Antihistamine:*** Astemizole, terfenadine ***Gastrointestinal:*** cisapride ***Psychotropic:*** midazolam, triazolam ***Ergot alkaloids:*** dihydroergotamine, ergotamine ***Herbs:*** St. John's wort, garlic supplements	***Antihistamine:*** astemizole, terfenadine ***Gastrointestinal:*** cisapride ***Psychotropic:*** midazolam, triazolam ***Ergot alkaloids:*** dihydroergotamine, ergotamine ***Herbs*:** St. John's wort, garlic supplements When SQV is used with low-dose RTV: ***Cardiac:*** flecainide, propafenone ***Neuroleptic:*** pimozide
-	-	Grapefruit juice increases SQV levels Dexamethasone decreases SQV levels

ANNEX 9. CHOICE OF ANTIRETROVIRAL DRUGS

Drug class	Pharmacokinetic issues	Toxicity issues
NsRTIs	ZDV, 3TC, d4T and ddI pharmacokinetics and dosing same as in non-pregnant person ABC not studied in pregnant women	Most data available in pregnant women on ZDV and 3TC Lactic acidosis/hepatic steatosis may be of special concern with use of d4T/ddI throughout pregnancy (although can occur with any NsRTI) Potential for mitochondrial toxicity in infant with *in utero* exposure (rare)
NNRTIs	Nevirapine pharmacokinetics in third trimester of pregnancy (no studies earlier in pregnancy) and dosing same as in non-pregnant person; half-life prolonged in labour Efavirenz not studied in pregnant women	Potential for teratogenicity with efavirenz (see text)
PIs	Nelfinavir 1250 mg given twice daily provides adequate levels in pregnant women Low-dose ritonavir boosting required with use of other PIs (indinavir or saquinavir) during pregnancy (inadequate drug levels in pregnancy without ritonavir boosting) Lopinavir/ritonavir not studied in pregnant women	Most data available concern pregnant women on nelfinavir Hyperglycaemia/diabetes mellitus a concern with PIs in pregnant women

IN HIV-INFECTED PREGNANT WOMEN

Prevention of mother-to-child HIV transmission	**Recommendations** (Note: All components of the antiretroviral regimen should be continued during labour)
ZDV alone and in combination with 3TC proven to reduce transmission All NsRTIs cross the placenta in varying amounts (ZDV, 3TC, d4T cross best)	ZDV/3TC first choice dual NsRTI backbone in pregnancy d4T/ddI used only if other dual NsRTIs have failed or produced unacceptable side-effects Be alert to early symptoms of lactic acidosis (gastrointestinal complaints worsening over time; tachypnoea; hepatomegaly; metabolic acidosis; elevated transaminases)
Nevirapine (single-dose) proven to reduce transmission NNRTIs cross the placenta, resulting in cord blood levels similar to maternal levels	Nevirapine is NNRTI choice for use in pregnancy Efavirenz should not be used in pregnancy (first trimester)
PIs do not cross placenta and are therefore unlikely to provide prophylaxis for infant, although reduction in viral load with HAART probably effective in lowering transmission risk	Nelfinavir first choice PI in pregnancy Saquinavir/ritonavir second choice PI in pregnancy Indinavir/ritonavir: theoretical concern about potential exacerbation of hyperbilirubinaemia in infant when administered near to/during labour Be alert to early symptoms of hyperglycaemia (increased urination/thirst, weight loss)

ANNEX 10. SUMMARY OF PAEDIATRIC DRUG FORMU

Name of drug	Formulations	Pharmacokinetic data available
Nucleoside analogue reverse transcriptase inhibitors		
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
Didanosine (ddI, dideoxyinosine)	Oral suspension paediatric powder/water: 10 mg/ml; In many countries needs to be made up with additional antacid Chewable tablets: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg Enteric-coated beadlets in capsules: 125 mg, 200 mg, 250 mg, 400 mg	All ages

LATIONS AND DOSES

	Age/weight, dose[a] and dose frequency	Other comments
	<4 weeks: 4 mg/kg/dose twice daily 4 weeks to 13 years: 180 mg/m^2/dose twice daily Maximum dose: ≥13years: 300 mg/dose twice daily	Large volume of syrup not well tolerated in older children Needs storage in glass jars and is light-sensitive Can be given with food Doses of 600 mg/m^2/dose twice daily required for HIV encephalopathy Do not use with d4T (antagonistic antiretroviral effect)
	<30 days: 2 mg/kg/dose twice daily ≥30 days or <60 kg: 4 mg/kg/dose twice daily Maximum dose: >60 kg: 150 mg/dose twice daily	Well tolerated Can be given with food Store solution at room temperature (use within one month of opening)
	Maximum dose: >13 yrs or >60 kg: 1 tablet/dose twice daily	Tablet should not be split
	<3 months: 50mg/m^2/dose twice daily ≥3 months to <13 yrs: 90 mg/m^2/dose twice daily or 240 mg/m^2/dose once daily Maximum dose: ≥13 yrs or >60 kg: 200 mg/dose twice daily or 400mg once daily	Keep suspension refrigerated; stable for 30 days; must be well shaken Ideally taken 1 hour before or 2 hours after food; may be less important in children Enteric-coated beadlets in capsules can be opened and sprinkled on small amount of food

Name of drug	Formulations	Pharmacokinetic data available
Nucleoside analogue reverse transcriptase inhibitors		
Stavudine (d4T)	Oral solution: 1 mg/ml Capsules: 15 mg, 20 mg, 30 mg, 40 mg	All ages
Abacavir (ABC)	Oral solution: 20 mg/ml Tablet: 300 mg	Over age 3 months
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
Nevirapine (NVP)	Oral suspension: 10 mg/ml Tablet: 200 mg	All ages

	Age/weight, dose[a] and dose frequency	Other comments
	<30kg: 1 mg/kg/dose twice daily 30 to 60 kg: 30 mg/dose twice daily Maximum dose: >60 kg: 40 mg/dose twice daily	Large volume of solution Keep solution refrigerated; stable for 30 days; must be well shaken. Needs to be stored in glass bottles Capsules opened up and mixed with small amount of food are well tolerated (stable in solution for 24 hours if kept refrigerated) Do not use with AZT (antagonistic antiretroviral effect)
	<16 years or <37.5 kg: 8 mg/kg/dose twice daily Maximum dose: >16 years or ≥37.5 kg: 300 mg/dose twice daily	Syrup well tolerated or tablet can be crushed Can be given with food PARENTS MUST BE WARNED ABOUT HYPERSENSITIVITY REACTION ABC should be stopped permanently if hypersensitivity reaction occurs
	Maximum dose: >40 kg: 1 tablet/dose twice daily	Tablet cannot be split PARENTS MUST BE WARNED ABOUT HYPERSENSITIVITY REACTION Abacavir should be stopped permanently if hypersensitivity reaction occurs
	15 to 30 days: 5 mg/kg/dose once daily for two weeks, then 120 mg/m^2/dose twice daily for two weeks, then 200 mg/m^2/dose twice daily >30 days to 13 years: 120 mg/m^2/dose twice daily for two weeks, then 200 mg/m^2/dose twice daily Maximum dose: >13 yrs: 200 mg/dose once daily for first two weeks, then 200 mg/dose twice daily	If rifampicin coadministration, increase NVP dose by ~30% or avoid use (see Chapter XII). Store suspension at room temperature; must be well shaken. Can be given with food 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 as from beginning of dose escalation; if severe rash, discontinue drug) Drug interactions

Name of drug	Formulations	Pharmacokinetic data available
Nucleoside analogue reverse transcriptase inhibitors		
Efavirenz (EFZ)	Syrup: 30 mg/ml (Note: syrup requires higher doses than capsules; see dosing chart) Capsules: 50 mg, 100 mg, 200 mg	Only for children over 3 years
Nelfinavir (NFV)	Powder for oral suspension (mix with liquid): 200 mg per level teaspoon (50 mg per 1.25-ml scoop): 5 ml Tablet: 250 mg (tablet can be halved; can be crushed and added to food or dissolved in water)	All ages; however, extensive pharmacokinetic variability in infants, with requirement for very high doses in infants <1 year
Lopinavir/ritonavir, (LPV/r)	Oral solution: 80 mg/ml lopinavir plus 20 mg/ml ritonavir Capsules: 133.3 mg lopinavir plus 33.3 mg ritonavir	6 months of age or older

[a] Metre^2 body surface area calculation: square root of (height in centimetres times weight in kilograms divided by 3600).

Age/weight, dose[a] and dose frequency	Other comments
Capsule (liquid) dose for >3 years: 10 to 15 kg: 200 mg (270 mg = 9 ml) once daily 15 to <20 kg: 250 mg (300 mg = 10 ml) once daily 20 to <25 kg: 300 mg (360 mg = 12 ml) once daily 25 to <33 kg: 350 mg (450 mg = 15 ml) once daily 33 to <40 kg: 400 mg (510 mg = 17 ml) once daily Maximum dose: ≥40 kg: 600mg once daily	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 Can be given with food (but avoid after high-fat meals which increase absorption by 50%) Best given at bedtime, especially for first two weeks, to reduce central nervous system side-effects Drug interactions
<1 year: 40-50 mg/kg/dose three times daily or 65-75 mg/kg/dose twice daily >1 year to <13 years: 55 to 65 mg/kg/dose twice daily Maximum dose: ≥13 years: 1250 mg/dose twice daily	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 (increases bitter taste) Because of difficulties with use of powder, use of crushed tablets preferred (even for infants) if appropriate dose can be given Powder and tablets can be stored at room temperature Take with food Drug interactions (less than ritonavir-containing protease inhibitors)
>6 months to 13 years: 225 mg/m^2 LPV/57.5 mg/m^2 ritonavir twice daily Or weight-based dosing: 7-15 kg: 12 mg/kg LPV/3 mg/ kg ritonavir/dose twice daily 15-40 kg: 10 mg/kg lopinavir/ 5 mg/kg ritonavir twice daily Maximum dose: >40 kg: 400 mg LPV/100 mg ritonavir (3 capsules or 5 ml) twice daily	Oral solution and capsules should preferably be refrigerated; however, can be stored at room temperature up to 25 °C (77 °F) for two months. Liquid formulation has low volume but bitter taste Preferably refrigerated Capsules large Should be taken with food Drug interactions

ANNEX 11A. ANTIRETROVIRAL DRUG TOXICITY

Nucleoside analogue reverse transcriptase inhibitors Drug class effects: nausea, with hepatic steatosis (potentially life-threatening); lipoatrophy; mitochondrial toxicity					
Antiretroviral drug	Category of adverse effects/toxicity				
	Haemato-logical	Hepatic	Pancreatic	Skin	Metabolic
Abacavir	+	+++	+	+++	Lactic acidosis
Didanosine	+	+++	+++	-	Lactic acidosis
Lamivudine	++	++	+++	++	Lactic acidosis
Stavudine	+	++++	++++	-	Lactic acidosis (more frequent than with other NsRTIs, especially if given with ddI and/or hydroxyurea)

vomiting; elevations in liver transaminases/hepatitis; lactic acidosis (e.g. myopathy, peripheral neuropathy)	
Nervous system	Comments
+	Potentially fatal hypersensitivity reaction in 5% (see text); usually occurs in first six weeks of treatment. Do not restart drug if hypersensitivity has occurred.
++++	Pancreatitis (possible increase in combination with d4T; can be fatal) and peripheral neuropathy most common. Nausea, diarrhoea (may be formulation-dependent). Retinal pigmentation (<5%, asymptomatic, seen in children) and optic neuritis have been reported. Potential increased risk of lactic acidosis/hepatic steatosis in pregnant women receiving ddI/d4T throughout pregnancy.
+++	Well tolerated; headache, abdominal pain. Pancreatitis may be more common in children who have advanced HIV disease. Peripheral neuropathy, neutropenia, elevated transaminases most common.
++++	Peripheral neuropathy, pancreatitis (may be increased with use in combination with ddI, rarely fatal) are the most common serious events. Gastrointestinal effects: nausea, vomiting, abdominal pain. Sleep disorders, increased energy/mania. Rare occurrence of ascending neuromuscular weakness resembling Guillain-Barre syndrome. Potential increased risk of lactic acidosis/hepatic steatosis in pregnant women receiving ddI/d4T throughout pregnancy.

Nucleoside analogue reverse transcriptase inhibitors Drug class effects: nausea, with hepatic steatosis (potentially life-threatening); lipoatrophy; mitochondrial toxicity

Antiretroviral drug	Category of adverse effects/toxicity				
	Haemato-logical	Hepatic	Pancreatic	Skin	Metabolic
Zidovudine	+++	++	-	-	Lactic acidosis

Non-nucleoside reverse transcriptase inhibitors Drug class effects: rash, hepatitis

Antiretroviral drug	Category of adverse effects/toxicity				
	Haemato-logical	Hepatic	Pancreatic	Skin	Metabolic
Efavirenz	+	++	-	++++	Lactic acidosis
Nevirapine	++	+++	-	++++	-

vomiting; elevations in liver transaminases/hepatitis; lactic acidosis (e.g. myopathy, peripheral neuropathy)	
Nervous system	Comments
-	Anaemia, neutropenia, increased transaminases most common. Macrocytosis almost 100%. Subjective complaints: gastrointestinal intolerance, headache, insomnia (common but self-limited). Blue to black discoloration of nails may occur. Myopathy 17%; cardiomyopathy rare.
Nervous system	Comments
Modest increases in triglycerides and cholesterol	Rash in ~10% of patients, but rarely severe (<1%), Stevens-Johnson syndrome very rare. Wide range of central nervous system problems (see text), often resolve in two to four weeks. Increased risk of liver toxicity if prior hepatitis B or C. Teratogenic in primates.
+	Rash occurs in ~16% of patients; rash may may be severe (8%); Stevens-Johnson syndrome or life-threatening rash seen in 0.3%. Use of two-week low-dose lead-in period (i.e. 200 mg once daily for two weeks, then escalation to 200 mg twice daily) reduces the incidence of rash. If mild to moderate rash occurs during dose escalation, ARVs should be discontinued until rash resolves; when ARVs are restarted, NVP should be restarted in the initial lead-in dosing phase. If mild to moderate rash occurs after the lead-in phase, NVP can be cautiously continued while rash observed or EFV can be substituted for NVP. If severe rash, mucosal lesions or systemic symptoms, NVP should be permanently discontinued and use of NNRTIs avoided. Increased risk of liver toxicity if prior hepatitis B or C; severe hepatitis, sometimes fatal, can occur. Drug interactions.

Non-nucleoside reverse transcriptase inhibitors Drug class effects: rash, hepatitis					
Antiretroviral drug	Category of adverse effects/toxicity				
	Haemato-logical	Hepatic	Pancreatic	Skin	Metabolic
Efavirenz	+	++	-	++++	Lactic acidosis
Nevirapine	++	+++	-	++++	-

Nervous system	Comments
Modest increases in triglycerides and cholesterol	Rash in ~10% of patients, but rarely severe (<1%), Stevens-Johnson syndrome very rare. Wide range of central nervous system problems (see text), often resolve in two to four weeks. Increased risk of liver toxicity if prior hepatitis B or C. Teratogenic in primates.
+	Rash occurs in ~16% of patients; rash may be severe (8%); Stevens-Johnson syndrome or life-threatening rash seen in 0.3%. Use of two-week low-dose lead-in period (i.e. 200 mg once daily for two weeks, then escalation to 200 mg twice daily) reduces the incidence of rash. If mild to moderate rash occurs during dose escalation, ARVs should be discontinued until rash resolves; when ARVs are restarted, NVP should be restarted in the initial lead-in dosing phase. If mild to moderate rash occurs after the lead-in phase, NVP can be cautiously continued while rash observed or EFV can be substituted for NVP. If severe rash, mucosal lesions or systemic symptoms, NVP should be permanently discontinued and use of NNRTIs avoided. Increased risk of liver toxicity if prior hepatitis B or C; severe hepatitis, sometimes fatal, can occur. Drug interactions.

Protease inhibitors *Drug class effects: insulin resistance, hyperglycaemia, new-onset diabetes mellitus including diabetic ketoacidosis; hyperlipidaemia (elevated triglyceride and cholesterol); fat redistribution (lipodystrophy); possible increased bleeding episodes in haemophiliacs; hepatitis; osteonecrosis, osteopenia/osteoporosis*

Antiretroviral drug	Category of adverse effects/toxicity				
	Haemato-logical	Hepatic	Pancreatic	Skin	Metabolic
Indinavir	+	+++	-	-	Lipid, glucose abnormalities
Lopinavir/ ritonavir	+	++	+	++	Lipid, glucose abnormalities
Nelfinavir	+	++	-	+	Lipid, glucose abnormalities
Saquinavir	+	++	-	+	Lipid, glucose abnormalities

Key:

- \- not reported or very rare
- \+ <1%
- ++ 1-4%
- +++ 5-9%
- ++++ >10%

Nervous system	Comments
-	Nephrolithiasis, 4-10%; adequate hydration must be ensured during therapy. Gastrointestinal intolerance, nausea 10-15%; oesophageal reflux in 3%. Indirect hyperbilirubinaemia, 10%. Subjective complaints: headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, Retinoid-like effects: alopecia, dry skin/lips, ingrown nails.
++	Gastrointestinal intolerance, nausea, diarrhoea, headache and asthenia most common. Oral solution contains 42% alcohol.
-	Diarrhoea common (10-30%) at start of therapy, often resolves on its own in a few days to weeks. Powder contains 11.2 mg phenylalanine per g.
-	Gastrointestinal intolerance, nausea, diarrhoea 10-20% (more common with soft gel), dyspepsia. Subjective symptoms: headache. Elevated transaminase enzymes.

ANNEX 11B. MONITORING AND MANAGEMENT

Antiretroviral drug	Primary toxicities
Nucleoside analogue reverse transcriptase inhibitors	See drug class effects for all drugs (text and Table 10)
Abacavir	Hypersensitivity reaction
Didanosine	Pancreatitis; painful peripheral neuropathy (dose-related, reversible); abdominal cramps, diarrhoea related to antacid in formulation
Lamivudine	Painful peripheral neuropathy; pancreatitis; headache, fatigue, insomnia; muscle aches; rash; rare neutropenia, thrombocytopenia
Stavudine	Painful peripheral neuropathy; pancreatitis; anaemia, macrocytosis; insomnia, anxiety, panic attacks

OF ANTIRETROVIRAL DRUG TOXICITY

Monitoring/management
Discontinue antiretroviral therapy if signs/symptoms of lactic acidosis/ hepatic steatosis. Following resolution of symptoms, ART can be restarted using a PI plus an NNRTI plus possibly either ABC or tenofovir. Other NsRTIs (ZDV, ddI, 3TC, d4T) should not be used.
Monitor for symptoms of hypersensitivity reaction. Hypersensitivity reaction is progressive; drug should be stopped; resolves once drug stopped. Do not rechallenge, as anaphylactic reactions and death reported.
Monitor for signs of neuropathy; consider drug discontinuation and change to another NsRTI (not d4T) if severe. Abdominal pain, nausea, vomiting should trigger evaluation for pancreatitis (serum pancreatic amylase, lipase). Discontinue therapy if confirmed; when resolves, restart and change to another NsRTI (not d4T). Clinical evaluation for signs of hepatitis (jaundice, hepatomegaly); monitor liver transaminases. Discontinue all therapy if confirmed, do not restart until resolves. Enteric coated capsules cause less diarrhoea and fewer drug interactions. ddI/d4T should not be given to pregnant women because of increased risk of lactic acidosis.
Abdominal pain, nausea, vomiting should trigger evaluation for pancreatitis (serum pancreatic amylase, lipase). Discontinue therapy if confirmed; when resolves, restart and change to another NsRTI (not ddI or d4T). Potential efficacy for hepatitis B infection (hepatitis flare-up may occur if 3TC is discontinued).
Monitor for signs of neuropathy; consider discontinuation or change to another NRTI (not ddI) if severe. Abdominal pain, nausea, vomiting should trigger evaluation for pancreatitis (serum pancreatic amylase, lipase). Discontinue therapy if confirmed; when resolves, restart and change to another NRTI (not ddI). Clinical evaluation for signs of hepatitis (jaundice, hepatomegaly); monitor liver transaminases. Discontinue all therapy if confirmed, do not restart until resolves, change to another NRTI. ddI/d4T should not be given to pregnant women because of increased risk of lactic acidosis.

Antiretroviral drug	Primary toxicities
Zidovudine	Initial headache, nausea common and self-limited; anaemia, granulocytopenia, thrombocytopenia; macrocytosis is expected effect of therapy, requires no intervention; myopathy (elevated creatinine phosphokinase may be seen) with long-term use; blue to black discoloration of nails in pigmented races.
Non-nucleoside reverse transcriptase inhibitors	
Efavirenz	Dizziness, anxiety, lightheadedness, dysphoria, nightmares; rash (less than with NVP); hepatitis.
Nevirapine	Rash, can be severe, Stevens-Johnson syndrome rare; fulminant hepatotoxicity rare.

Monitoring/management
Clinical examination for signs of anaemia. Monitor complete blood count with differential for haematological toxicity; for severe anaemia or neutropenia (absolute neutrophil count <500/ml), reduce ZDV dose if needed or change to another NsRTI; transfusions can be used for severe anaemia if ZDV therapy required. Check creatinine phosphokinase if muscle weakness/pain; consider discontinuation of ZDV or change to another NsRTI if severe.
Clinical evaluation for rash; rash from one NNRTI does not predict cross-reaction with other. Clinical evaluation for signs of hepatitis (jaundice, hepatomegaly); monitor liver transaminases. Discontinue all therapy if confirmed, do not restart until resolves.
Clinical evaluation for rash; rash from one NNRTI does not predict cross-reaction with other. Low-dose lead-in period over first two weeks minimizes rash occurrence. If rash is mild or moderate, NVP can be continued cautiously while the rash is observed or EFZ can be substituted for NVP. Do not increase dose during lead-in phase if rash; stop drugs and restart NVP at lead-in dosing when resolves. Permanently discontinue NVP if rash severe, and avoid NNRTI class of drugs. Clinical evaluation for signs of hepatitis (jaundice, hepatomegaly); monitor liver transaminases. Discontinue all therapy if confirmed, do not restart until resolves; permanently discontinue NVP if hepatitis (changing NNRTI to EFZ can be tried).

Antiretroviral drug	Primary toxicities
Protease inhibitors	See drug class effects for all drugs (text and Table 10).
Indinavir	Nephrolithiasis, crystalluria, haematuria, rare interstitial nephritis; asymptomatic hyperbilirubinaemia; nausea, gastrointestinal disturbances; rash; insomnia, dizziness, metallic taste; alopecia, dry skin; thrombocytopenia.
Lopinavir/ritonavir	Diarrhoea; skin rash; headache, weakness
Nelfinavir	Diarrhoea, gastrointestinal disturbance.
Saquinavir	Diarrhoea; headache confusion.

Monitoring/management
Monitor for symptoms of hyperglycaemia (polydipsia/polyuria/polyphagia), urine dipstick for glucose. Clinical evaluation for signs of hepatitis (jaundice, hepatomegaly); monitor liver transaminases. Discontinue all therapy if confirmed, do not restart until resolves. Consider avascular necrosis in patients presenting with hip or shoulder pain, limp.
Drink at least 1.5 litres of fluids per day. Monitor urinanalysis for haematuria. Evaluate if flank pain, possibly temporarily discontinue IDV, restart after resolves (recurrent nephrolithiasis in 50%). Hyperbilirubinaemia clinically insignificant.
Diarrhoea mild.
Diarrhoea is self-limited; can be controlled with loperamide, calcium carbonate, psyllium, oat bran.
Generally well tolerated with low-dose ritonavir boost to provide higher levels.

REFERENCES

1. Piot P, Bartos M, Ghys PD, Walker N, Schwartlander B. The global impact of HIV/AIDS. *Nature* 2001;410:968-73.
2. Sepkowitz KA. AIDS - the first 20 years. *N Engl J Med* 2001;344:1764-72.
3. Gayle HD, Hill GL. Global impact of human immunodeficiency virus and AIDS. *Clin Microbiol Rev* 2001;14:327-35.
4. Fauci AS. The AIDS epidemic - considerations for the 21st century. *N Engl J Med* 1999;341:1046-50.
5. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 38:853-60.
6. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet* 1998;352:1725-30.
7. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet* 2000;356:291-6.
8. Lavalle C, Aguilar JC, Pena F, Estrada-Aguilar JL, Avina-Zubieta JA, Madrazo M. Reduction in hospitalization costs, morbidity, disability, and mortality in patients with aids treated with protease inhibitors. *Arch Med Res* 2000;31:515-9.
9. Caride E, Brindeiro R, Hertogs K, et al. Drug-resistant reverse transcriptase genotyping and phenotyping of B and non-B subtypes (F and A) of human immunodeficiency virus type I found in Brazilian patients failing HAART. *Virology* 2000;275:107-15.
10. Schwartlander B, Stover J, Walker N, et al. AIDS. Resource needs for HIV/AIDS. *Science* 2001;292:2434-6.
11. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000;342:921-9.
12. Chakraborty H, Sen PK, Helms RW, et al. Viral burden in genital secretions determines male-to-female sexual transmission of HIV-1: a probabilistic empiric model. *AIDS* 2001;15:621-7.
13. Carpenter CC, Cooper DA, Fischl MA, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. *JAMA* 2000;283:381-90.
14. Delfraissy JF. New French guidelines for antiretroviral treatment. *HIV Med* 2000;1:133-6.
15. BHIVA. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. *HIV Med* 2001;2:276-313.
16. USPHS/Kaiser. *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, 2002.* http://www.hivatis.org/guidelines/adult/Feb04_02/AdultGdl.pdf
17. Havlir DV, Richman DD. The role of viral dynamics in the pathogenesis of HIV disease and implications for antiviral therapy. *Springer Semin Immunopathol* 1997;18:267-83.

18. Havlir DV, Richman DD. Viral dynamics of HIV: implications for drug development and therapeutic strategies. *Ann Intern Med* 1996;124:984-94.
19. Perelson AS, Essunger P, Ho DD. Dynamics of HIV-1 and CD4+ lymphocytes in vivo. *AIDS* 1997;11(Suppl A):S17-24.
20. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996; 271:1582-6.
21. Ramratnam B, Bonhoeffer S, Binley J, et al. Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis. *Lancet* 1999;354:1782-5.
22. Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 1995;373:117-22.
23. Wu H, Ding AA, De Gruttola V. Estimation of HIV dynamic parameters. *Stat Med* 1998;17:2463-85.
24. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995;373:123-6.
25. Jordan R, Gold L, Cummins C, Hyde C. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *BMJ* 2002;324:757-60.
26. Bidwell Goetz M, Morreale AP, Rhew DC, et al. Effect of highly active antiretroviral therapy on outcomes in Veterans Affairs Medical Centers. *AIDS* 2001;15:530-2.
27. Beck EJ, Mandalia S, Williams I, et al. Decreased morbidity and use of hospital services in English HIV-infected individuals with increased uptake of anti-retroviral therapy 1996-1997. National Prospective Monitoring System Steering Group. *AIDS* 1999;13:2157-64.
28. Floridia M, Massella M, Bucciardini R, et al. Hospitalizations and costs of treatment for protease inhibitor-based regimens in patients with very advanced HIV-infection (CD4 < 50/mm^3). *HIV Clin Trials* 2000;1:9-16.
29. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997;337:734-9.
30. Gulick RM, Mellors JW, Havlir D, et al. 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Ann Intern Med* 2000;133:35-9.
31. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N Engl J Med* 1997;337:725-33.
32. Hogg RS, Yip B, Kully C, et al. Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *Cmaj* 1999;160:659-65.
33. Keiser P, Nassar N, Kvanli MB, Turner D, Smith JW, Skiest D. Long-term impact of highly active antiretroviral therapy on HIV-related health care costs. *J Acquir Immune Defic Syndr* 2001;27:14-9.

34. Le Pen C, Rozenbaum W, Downs A, Maurel F, Lilliu H, Brun C. Effect of HAART on health status and hospital costs of severe HIV-infected patients: a modeling approach. *HIV Clin Trials* 2001;2:136-45.
35. Matthews GV, Sabin CA, Mandalia S, et al. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. *AIDS* 2002;16:53-61.
36. Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, the Netherlands, Canada and Australia Study. *JAMA* 1998;279:930-7.
37. Powderly WG, Saag MS, Chapman S, Yu G, Quart B, Clendeninn NJ. Predictors of optimal virological response to potent antiretroviral therapy. *AIDS* 1999;13:1873-80.
38. Montaner JS, Harris M, Mo T, Harrigan PR. Rebound of plasma HIV viral load following prolonged suppression with combination therapy. *AIDS* 1998;12:1398-9.
39. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA* 2001;285:1155-63.
40. Gunthard HF, Wong JK, Ignacio CC, et al. Human immunodeficiency virus replication and genotypic resistance in blood and lymph nodes after a year of potent antiretroviral therapy. *J Virol* 1998;72:2422-8.
41. Wong JK, Gunthard HF, Havlir DV, et al. Reduction of HIV-1 in blood and lymph nodes following potent antiretroviral therapy and the virologic correlates of treatment failure. *Proc Natl Acad Sci U S A* 1997;94:12574-9.
42. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999;341:1865-73.
43. Demeter LM, Hughes MD, Coombs RW, et al. Predictors of virologic and clinical outcomes in HIV-1-infected patients receiving concurrent treatment with indinavir, zidovudine, and lamivudine. AIDS Clinical Trials Group Protocol 320. *Ann Intern Med* 2001;135:954-64.
44. Piot P, Coll Seck AM. International response to the HIV/AIDS epidemic: planning for success. *Bull World Health Organ* 2001;79:1106-12.
45. Tanuri A, Vicente AC, Otsuki K, et al. Genetic variation and susceptibilities to protease inhibitors among subtype B and F isolates in Brazil. *Antimicrob Agents Chemother* 1999;43:253-8.
46. Becker-Pergola G, Kataaha P, Johnston-Dow L, Fung S, Jackson JB, Eshleman SH. Analysis of HIV type 1 protease and reverse transcriptase in antiretroviral drug-naive Ugandan adults. *AIDS Res Hum Retroviruses* 2000;6:807-13.
47. Weidle PJ, Kityo CM, Mugyenyi P, et al. Resistance to antiretroviral therapy among patients in Uganda. *J Acquir Immune Defic Syndr* 2001;26:495-500.

48. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001;286:2568-77.
49. Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. *JAMA* 2001;286:2560-7.
50. Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. *AIDS* 2001;15:2251-7.
51. Cozzi Lepri A, Phillips AN, d'Arminio Monforte A, et al. When to start highly active antiretroviral therapy in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 2001;15:983-90.
52. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. *Ann Intern Med* 1999;130:570-7.
53. Beck EJ, Kupek EJ, Gompels MM, Pinching AJ. Correlation between total and CD4 lymphocyte counts in HIV infection: not making the good an enemy of the not so perfect. *Int J STD AIDS* 1996;7:422-8.
54. Fournier AM, Sosenko JM. The relationship of total lymphocyte count to CD4 lymphocyte counts in patients infected with human immunodeficiency virus. *Am J Med Sci* 1992;304:79-82.
55. Gebo KA, Chaisson RE, Folkemer JG, Bartlett JG, Moore RD. Costs of HIV medical care in the era of highly active antiretroviral therapy. *AIDS* 1999;13:963-9.
56. van der Ryst E, Kotze M, Joubert G, et al. Correlation among total lymphocyte count, absolute CD4+ count, and CD4+ percentage in a group of HIV-1-infected South African patients. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:238-44.
57. Schechter M, Zajdenverg R, Machado LL, Pinto ME, Lima LA, Perez MA. Predicting CD4 counts in HIV-infected Brazilian individuals: a model based on the World Health Organization staging system. *J Acquir Immune Defic Syndr* 1994;7:163-8.
58. French N, Mujugira A, Nakiyingi J, Mulder D, Janoff EN, Gilks CF. Immunologic and clinical stages in HIV-1-infected Ugandan adults are comparable and provide no evidence of rapid progression but poor survival with advanced disease. *J Acquir Immune Defic Syndr* 1999;22:509-16.
59. Lima LA, May SB, Perez MA, Schechter M. Survival of HIV-infected Brazilians: a model based on the World Health Organization staging system. *AIDS* 1993;7:295-6.
60. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;126:946-54.
61. Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis* 1998;177:40-7.
62. Phillips AN, Pradier C, Lazzarin A, et al. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients. *AIDS* 2001;15:2385-95.

63. Casado JL, Dronda F, Hertogs K, et al. Efficacy, tolerance, and pharmacokinetics of the combination of stavudine, nevirapine, nelfinavir, and saquinavir as salvage regimen after ritonavir or indinavir failure. *AIDS Res Hum Retroviruses* 2001;17:93-8.
64. van der Valk M, Kastelein JJ, Murphy RL, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS* 2001;15:2407-14.
65. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. *AIDS* 2001;15:1369-77.
66. Katlama C, Valantin MA, Matheron S, et al. Efficacy and tolerability of stavudine plus lamivudine in treatment-naive and treatment-experienced patients with HIV-1 infection. *Ann Intern Med* 1998;129:525-31.
67. Kuritzkes DR, Marschner I, Johnson VA, et al. Lamivudine in combination with zidovudine, stavudine, or didanosine in patients with HIV-1 infection. A randomized, double-blind, placebo-controlled trial. National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group Protocol 306 Investigators. *AIDS* 1999;13:685-94.
68. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect* 2002;78:58-9.
69. Chene G, Angelini E, Cotte L, et al. Role of long-term nucleoside-analogue therapy in lipodystrophy and metabolic disorders in human immunodeficiency virus-infected patients. *Clin Infect Dis* 2002;34:649-57.
70. van der Valk M, Gisolf EH, Reiss P, et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2001;15:847-55.
71. Moyle G. Toxicity of antiretroviral nucleoside and nucleotide analogues: is mitochondrial toxicity the only mechanism? *Drug Saf* 2000;23:467-81.
72. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidaemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000;14:F25-32.
73. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Delta Coordinating Committee. *Lancet* 1996;348:283-91.
74. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. *N Engl J Med* 1996;335:1081-90.
75. Eron JJ. The treatment of antiretroviral-naive subjects with the 3TC/zidovudine combination: a review of North American (NUCA 3001) and European (NUCB 3001) trials. *AIDS* 1996;10(Suppl 5):S11-9.

76. Hogg RS, Rhone SA, Yip B, et al. Antiviral effect of double and triple drug combinations amongst HIV-infected adults: lessons from the implementation of viral load-driven antiretroviral therapy. *AIDS* 1998;12:279-84.
77. Havlir DV, Tierney C, Friedland GH, et al. In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000;182:321-5.
78. Mangum EM, Graham KK. Lopinavir-Ritonavir: a new protease inhibitor. *Pharmacotherapy* 2001;21:1352-63.
79. Daluge SM, Good SS, Faletto MB, et al. 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. *Antimicrob Agents Chemother* 1997;41:1082-93.
80. van Heeswijk RP, Veldkamp A, Mulder JW, et al. Combination of protease inhibitors for the treatment of HIV-1-infected patients: a review of pharmacokinetics and clinical experience. *Antivir Ther* 2001;6:201-29.
81. Qazi NA, Morlese JF, Pozniak AL. Lopinavir/ritonavir (ABT-378/r). *Expert Opin Pharmacother* 2002;3:315-27.
82. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. *AIDS* 2000;14:F83-93.
83. Jarvis B, Faulds D. Nelfinavir. A review of its therapeutic efficacy in HIV infection. *Drugs* 1998;56:147-67.
84. Patick AK, Duran M, Cao Y, et al. Genotypic and phenotypic characterization of human immunodeficiency virus type 1 variants isolated from patients treated with the protease inhibitor nelfinavir. *Antimicrob Agents Chemother* 1998;42:2637-44.
85. Hirsch M, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis* 1999;180:659-65.
86. Holstein A, Plaschke A, Egberts EH. Lipodystrophy and metabolic disorders as complication of antiretroviral therapy of HIV infection. *Exp Clin Endocrinol Diabetes* 2001;109:389-92.
87. Herman JS, Easterbrook PJ. The metabolic toxicities of antiretroviral therapy. *Int J STD AIDS* 2001;12:555-62; quiz 563-4.
88. Behrens GM, Meyer D, Stoll M, Schmidt RE. Immune reconstitution syndromes in human immuno-deficiency virus infection following effective antiretroviral therapy. *Immunobiology* 2000;202:186-93.
89. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA* 2000;283:229-34.
90. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team). *JAMA* 2000;283:205-11.

91. Sugiura W, Matsuda Z, Yokomaku Y, et al. Interference between D30N and L90M in selection and development of protease inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2002;46:708-15.
92. Harrigan PR, Stone C, Griffin P, et al. Resistance profile of the human immunodeficiency virus type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. CNA2001 Investigative Group. *J Infect Dis* 2000;181:912-20.
93. Miller V, Ait-Khaled M, Stone C, et al. HIV-1 reverse transcriptase (RT) genotype and susceptibility to RT inhibitors during abacavir monotherapy and combination therapy. *AIDS* 2000;14:163-71.
94. Miller V, Larder BA. Mutational patterns in the HIV genome and cross-resistance following nucleoside and nucleotide analogue drug exposure. *Antivir Ther* 2001;6(Suppl 3):25-44.
95. Miller V, Sturmer M, Staszewski S, et al. The M184V mutation in HIV-1 reverse transcriptase (RT) conferring lamivudine resistance does not result in broad cross-resistance to nucleoside analogue RT inhibitors. *AIDS* 1998;12:705-12.
96. Walter H, Schmidt B, Werwein M, Schwingel E, Korn K. Prediction of abacavir resistance from genotypic data: impact of zidovudine and lamivudine resistance in vitro and in vivo. *Antimicrob Agents Chemother* 2002;46:89-94.
97. Martinez-Picado J, DePasquale MP, Kartsonis N, et al. Antiretroviral resistance during successful therapy of HIV type 1 infection. *Proc Natl Acad Sci U S A* 2000;97:10948-53.
98. Frater AJ, Beardall A, Ariyoshi K, et al. Impact of baseline polymorphisms in RT and protease on outcome of highly active antiretroviral therapy in HIV-1-infected African patients. *AIDS* 2001;15:1493-502.
99. Holguin A, Rodes B, Soriano V. Protease gene analysis of HIV type 1 non-B subtypes in Spain. *AIDS Res Hum Retroviruses* 2000;16:1395-403.
100. Perez-Alvarez L, Cuevas MT, Villahermosa ML, et al. Prevalence of drug resistance mutations in B, non-B subtypes, and recombinant forms of human immunodeficiency virus type 1 in infected individuals in Spain (Galicia). *J Hum Virol* 2001;4:35-8.
101. Pieniazek D, Rayfield M, Hu DJ, et al. Protease sequences from HIV-1 group M subtypes A-H reveal distinct amino acid mutation patterns associated with protease resistance in protease inhibitor-naive individuals worldwide. HIV Variant Working Group. *AIDS* 2000; 4:1489-95.
102. Quinones-Mateu ME, Albright JL, Mas A, Soriano V, Arts EJ. Analysis of pol gene heterogeneity, viral quasispecies, and drug resistance in individuals infected with group O strains of human immunodeficiency virus type 1. *J Virol* 1998;72:9002-15.
103. Ruibal-Brunet IJ, Cuevas MT, Diaz-Torres H, et al. Genotypic resistance mutations to antiretroviral drugs in HIV-1 B and non-B subtypes from Cuba. *Rev Panam Salud Publica* 2001;10:174-80.
104. Yerly S, Vora S, Rizzardi P, et al. Acute HIV infection: impact on the spread of HIV and transmission of drug resistance. *AIDS* 2001;15:2287-92.

105. Taylor GP, Low-Beer N. Antiretroviral therapy in pregnancy: a focus on safety. *Drug Saf* 2001;24:683-702.
106. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. *Lancet* 1999;353:773-80.
107. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet* 1999;353:781-5.
108. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Côte d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. *Lancet* 1999;353:786-92.
109. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* 1999;354:795-802.
110. Gray G. *The PETRA study: early and late efficacy of three short AZT/3TC combination regimens to prevent mother-to-child transmission of HIV-1.* XIII International AIDS Conference, Durban, South Africa, 9-14 July 2000.
111. Garcia P, Beckerman K, Watts H. *Assessing the teratogenic potential of antiretroviral drugs: data from the Antiretroviral Pregnancy Registry.* 41st Conference on Antimicrobial Agents and Chemotherapy., Chicago, IL, 16-19 December 2001.
112. Nightingale SL. From the Food and Drug Administration. *JAMA* 1998;280:1472.
113. USPHS. Recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States, 2002. http://www.hivatis.org/guidelines/perinatal/Feb4_02/Perin.pdf
114. De Santis M, Carducci B, De Santis L, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. *Arch Intern Med* 2002;162:355.
115. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002;16:299-300.
116. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;331:1173-80.
117. O'Sullivan MJ, Boyer PJ, Scott GB, et al. The pharmacokinetics and safety of zidovudine in the third trimester of pregnancy for women infected with human immunodeficiency virus and their infants: phase I acquired immunodeficiency syndrome clinical trials group study (protocol 082). Zidovudine Collaborative Working Group. *Am J Obstet Gynecol* 1993;168:1510-6.

118. Wang Y, Livingston E, Patil S, et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected pregnant women and their neonates: an AIDS clinical trials group study. *J Infect Dis* 1999;180:1536-41.
119. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis* 1998;178:1327-33.
120. Boxwell D, BA BS. *Lactic acidosis (LA) in patients receiving nucleoside analogue reverse transcriptase inhibitors (NRTIs).* 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 26-29 September 1999.
121. Grimbert S, Fisch C, Deschamps D, et al. Effects of female sex hormones on mitochondria: possible role in acute fatty liver of pregnancy. *Am J Physiol* 1995;268:G107-15.
122. Grimbert S, Fromenty B, Fisch C, et al. Decreased mitochondrial oxidation of fatty acids in pregnant mice: possible relevance to development of acute fatty liver of pregnancy. *Hepatology* 1993;17:628-37.
123. Luzzati R, Del Bravo P, Di Perri G, Luzzani A, Concia E. Riboflavine and severe lactic acidosis. *Lancet* 1999;353:901-2.
124. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;354:1084-9.
125. Lipshultz SE, Easley KA, Orav EJ, et al. Absence of cardiac toxicity of zidovudine in infants. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study Group. *N Engl J Med* 2000;343:759-66.
126. Bulterys M, Nesheim S, Abrams EJ, et al. Lack of evidence of mitochondrial dysfunction in the offspring of HIV-infected women. Retrospective review of perinatal exposure to antiretroviral drugs in the Perinatal AIDS Collaborative Transmission Study. *Ann N Y Acad Sci* 2000;918:212-21.
127. Committee APRS. *Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2001.* Wilmington NC: Registry Project Office; 2001.
128. Musoke P, Guay LA, Bagenda D, et al. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). *AIDS* 1999;13:479-86.
129. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet* 2000;39:281-93.
130. Mirochnick M, Fenton T, Gagnier P, et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *J Infect Dis* 1998;178:368-74.
131. Morris AB, Cu-Uvin S, Harwell JI, et al. Multicenter review of protease inhibitors in 89 pregnancies. *J Acquir Immune Defic Syndr* 2000;25:306-11.

132. Reiss G, O'Brien M, Kopicko J, Clark RA. Lack of association between pregnancy and selected gastrointestinal adverse events among women prescribed nelfinavir. *J Acquir Immune Defic Syndr* 2001;26:513-4.
133. Bryson Y, Stek A, Mirochnick M, et al. *Pharmacokinetics, antiviral activity and safety of nelfinavir (NFV) in combination with ZDV/3TC in pregnant HIV-infected women and their infants: PACTG 353 cohort 2.* 9th Conference on Retroviruses and Opportunistic Infections, Seattle, WA, 24-28 February 2002. In press.
134. Acosta EP, Zorrilla C, Van Dyke R, et al. Pharmacokinetics of saquinavir-SGC in HIV-infected pregnant women. *HIV Clin Trials* 2001;2:460-5.
135. Angel JB, Khaliq Y, Monpetit ML, Cameron DW, Gallicano K. An argument for routine therapeutic drug monitoring of HIV-1 protease inhibitors during pregnancy. *AIDS* 2001;15:417-9.
136. Hayashi S, Beckerman K, Homma M, Kosel BW, Aweeka FT. Pharmacokinetics of indinavir in HIV-positive pregnant women. *AIDS* 2000;14:1061-2.
137. Wara D, Tuomala R, Bryson Y, et al. *PACTG 358 - Safety, pharmacokinetic and antiretroviral activity of indinavir (IDV), zidovudine (ZDV) and lamivudine (3TC) in HIV-1-seropositive pregnant women and infants.* Global Strategies for the Prevention of HIV Transmission from Mothers to Infants, Montreal, Canada, 1999.
138. Eshleman SH, Mracna M, Guay LA, et al. Selection and fading of resistance mutations in women and infants receiving nevirapine to prevent HIV-1 vertical transmission (HIVNET 012). *AIDS* 2001;15:1951-7.
139. Eshleman SH, Becker-Pergola G, Deseyve M, et al. Impact of human immunodeficiency virus type 1 (HIV-1) subtype on women receiving single-dose nevirapine prophylaxis to prevent HIV-1 vertical transmission (HIV network for prevention trials 012 study). *J Infect Dis* 2001;184:914-7.
140. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001;285:2083-93.
141. Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstet Gynecol* 2000;95:167-73.
142. Turner BJ, Newschaffer CJ, Zhang D, Cosler L, Hauck WW. Antiretroviral use and pharmacy-based measurement of adherence in postpartum HIV-infected women. *Med Care* 2000;38:911-25.
143. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS* 1995;9:F7-11.

144. Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial Study Group. *J Infect Dis* 1997;175:1029-38.
145. Duong T, HIV Paediatric Prognostic Markers Collaborative Study Group. *Predictive value of CD4 count and viral load for disease progression in untreated HIV-infected children.* XIV International AIDS Conference, Barcelona, Spain, 7-11 July 2002.
146. Shearer WT, Quinn TC, Lew J, NIH NIAID/NICHD/NIDA-Sponsored Women and Infants Transmission Study Group. High infant HIV-1 RNA plasma load associated with disease progression and death in the Women and Infants Transmission Study. *N Engl J Med* 1997;336:1337-42.
147. Wade AM, Ades AE. Age-related reference ranges: significance tests for models and confidence intervals for centiles. *Stat Med* 1994;13:2359-67.
148. Dunn D, Newell ML, Ades T, Peckham C, Maria AD. CD4 T cell count as predictor of *Pneumocystis carinii* pneumonia in children born to mothers infected with HIV. *BMJ* 1994;308:437-40.
149. DeRossi A, Walker A, Klein N, et al. Increased thymic output after initiation of antiretroviral therapy in HIV-1-infected children in the PENTA 5 trial. *J Infect Dis* 2002;in press.
150. Tovo PA, de Martino M, Gabiano C, et al. Prognostic factors and survival in children with perinatal HIV-1 infection. The Italian Register for HIV Infections in Children. *Lancet* 1992;339:1249-53.
151. Luzuriaga K, McManus M, Catalina M, et al. Early therapy of vertical human immunodeficiency virus type 1 (HIV-1) infection: control of viral replication and absence of persistent HIV-1-specific immune responses. *J Virol* 2000;74:6984-91.
152. Compagnucci A, Saidi Y, Chaix, et al., PENTA. *Difficulties in achieving suppression of viral replication in vertically HIV-1 infected infants treated early with d4T+ddI+NFV – The PENTA 7 Study.* Ninth Conference on Retrovirus and Opportunistic Infections. Seattle, February 2002; Abstract 809W (see also http://www.ctu.mrc.ac.uk/PENTA).
153. Committee PS. *PENTA Guidelines for the use of Antiretroviral Therapy in Paediatric HIV Infection - 2001*. 2001. http://www.ctu.mrc.ac.uk/PENTA/
154. USPHS. Guidelines for the use of antiretroviral agents in pediatric HIV-infection, 2001. http://www.hivatis.org/guidelines/Pediatric/Dec12_01/peddec.pdf
155. Taha TE, Graham SM, Kumwenda NI, et al. Morbidity among human immunodeficiency virus-1-infected and -uninfected African children. *Pediatrics* 2000;106:E77.
156. Spira R, Lepage P, Msellati P, et al. Natural history of human immunodeficiency virus type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. *Pediatrics* 1999;104:E56.

157. Mofenson L, Harris D, Moye J, et al. *Low technology predictors of mortality for resource-poor settings: association of total lymphocyte count (TLC) and white blood cell count (WBC) with mortality in HIV-1-infected children.* XIV International AIDS Conference, Barcelona, Spain, 7-11 July 2002.
158 Paediatric European Network for Treatment of AIDS. Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet* 2002;359:733-40.
159. Lindsey JC, Hughes MD, McKinney RE, et al. Treatment-mediated changes in human immunodeficiency virus (HIV) type 1 RNA and CD4 cell counts as predictors of weight growth failure, cognitive decline, and survival in HIV-infected children. *J Infect Dis* 2000;182:1385-93.
160. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999;282:677-86.
161. Santoro-Lopes G, de Pinho AM, Harrison LH, Schechter M. Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. *Clin Infect Dis* 2002;34:543-6.
162. Harries AD, Hargreaves NJ, Kemp J, et al. Deaths from tuberculosis in sub-Saharan African countries with a high prevalence of HIV-1. *Lancet* 2001;357:1519-23.
163. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001;164:7-12.
164. Wagner KR, Bishai WR. Issues in the treatment of *Mycobacterium tuberculosis* in patients with human immunodeficiency virus infection. *AIDS* 2001;15(Suppl 5):S203-12.
165. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 1999;340:367-73.
166. Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS* 2002;16:75-83.
167. Lopez-Cortes LF, Ruiz R, P.Viciana, et al. *Pharmacokinetic interactions between rifampin and efavirenz in patients with tuberculosis and HIV infection.* 8th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, 2001.
168. Ribera E, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acquir Immune Defic Syndr* 2001;28:450-3.
169. Veldkamp AI, Hoetelmans RM, Beijnen JH, Mulder JW, Meenhorst PL. Ritonavir enables combined therapy with rifampin and saquinavir. *Clin Infect Dis* 1999;29:1586.
170. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1-associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* 1998;351:256-61.

171. Chung RT, Kim AY, Polsky B. HIV/Hepatitis B and C coinfection: pathogenic interactions, natural history and therapy. *Antivir Chem Chemother* 2001;12(Suppl 1):73-91.
172. Ying C, De Clercq E, Neyts J. Lamivudine, adefovir and tenofovir exhibit long-lasting anti-hepatitis B virus activity in cell culture. *J Viral Hepat* 2000;7:79-83.
173. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med* 1999;341:1256-63.
174. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med* 2000;133:447-54.
175. Cheng VC, Yuen KY, Chan WM, Wong SS, Ma ES, Chan RM. Immunorestitution disease involving the innate and adaptive response. *Clin Infect Dis* 2000;30:882-92.
176. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998;158:157-61.
177. USPHS/IDSA. *2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with HIV, 2001.* http://www.hivatis.org/guidelines/other/OIs/OIGNov27.pdf
178. Quigley MA, Mwinga A, Hosp M, et al. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian adults. *AIDS* 2001;15:215-22.
179. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS* 2001;15:2137-47.
180. Bucher HC, Griffith LE, Guyatt GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *AIDS* 1999;13:501-7.
181. Wilkinson D, Squire SB, Garner P. Effect of preventive treatment for tuberculosis in adults infected with HIV: systematic review of randomised placebo controlled trials. *BMJ* 1998;317:625-9.
182. Pezzotti P, Phillips AN, Dorrucci M, et al. Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion. HIV Italian Seroconversion Study Group. *BMJ* 1996;313:583-6.
183. Eskild A, Magnus P, Sohlberg C, et al. Slow progression to AIDS in intravenous drug users infected with HIV in Norway. *J Epidemiol Community Health* 1994;48:383-7.
184. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. *N Engl J Med* 1995;333:751-6.
185. McGlothlin WH, Anglin MD. Long-term follow-up of clients of high- and low-dose methadone programs. *Arch Gen Psychiatry* 1981;38:1055-63.
186. Dole VP, Robinson JW, Orraca J, Towns E, Searcy P, Caine E. Methadone treatment of randomly selected criminal addicts. *N Engl J Med* 1969;280:1372-5.

187. Des Jarlais DC, Friedman SR, Novick DM, et al. HIV-1 infection among intravenous drug users in Manhattan, New York City, from 1977 through 1987. *JAMA* 1989;261:1008-12.
188. Grabowski J, Rhoades H, Schmitz J, et al. Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *J Clin Psychopharmacol* 2001;21:522-6.
189. Bangsberg DR, Hecht FM, Clague H, et al. Provider assessment of adherence to HIV antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001;26:435-42.
190. Catz SL, Kelly JA, Bogart LM, Benotsch EG, McAuliffe TL. Patterns, correlates, and barriers to medication adherence among persons prescribed new treatments for HIV disease. *Health Psychol* 2000;19:124-33.
191. DeMasi RA, Graham NM, Tolson JM, et al. Correlation between self-reported adherence to highly active antiretroviral therapy (HAART) and virologic outcome. *Adv Ther* 2001;18:163-73.
192. Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bull World Health Organ* 2001;79:1145-51.
193. Farmer P, Leandre F, Mukherjee JS, et al. Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001;358:404-9.
194. Giron-Gonzalez JA, Lopez-Sanchez A, Elvira J, Perez E, Fernandez-Gutierrez C. Effect of patient adherence to antiretroviral therapy on CD4+ cell count, HIV-1 RNA, and serum concentrations of tumor necrosis factor and its soluble receptors. *Eur J Clin Microbiol Infect Dis* 2000;19:852-8.
195. Greenberg B, Berkman A, Thomas R, et al. Evaluating supervised HAART in late-stage HIV among drug users: a preliminary report. *J Urban Health* 1999;76:468-80.
196. Gross R, Bilker WB, Friedman HM, Strom BL. Effect of adherence to newly initiated antiretroviral therapy on plasma viral load. *AIDS* 2001;15:2109-17.
197. Haubrich RH, Little SJ, Currier JS, et al. The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group. *AIDS* 1999;13:1099-107.
198. Knobel H, Carmona A, Grau S, Pedro-Botet J, Diez A. Adherence and effectiveness of highly active antiretroviral therapy. *Arch Intern Med* 1998;158:1953.
199. Knobel H, Guelar A, Carmona A, et al. Virologic outcome and predictors of virologic failure of highly active antiretroviral therapy containing protease inhibitors. *AIDS Patient Care STDS* 2001;15:193-9.
200. McNabb J, Ross JW, Abriola K, Turley C, Nightingale CH, Nicolau DP. Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic.

Clin Infect Dis 2001;33:700-5.
201. Mocroft A, Madge S, Johnson AM, et al. A comparison of exposure groups in the EuroSIDA study: starting highly active antiretroviral therapy (HAART), response to HAART, and survival. *J Acquir Immune Defic Syndr* 1999;22:369-78.
202. Nieuwkerk PT, Sprangers MA, Burger DM, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. *Arch Intern Med* 2001;161:1962-8.
203. Paris D, Ledergerber B, Weber R, et al. Incidence and predictors of virologic failure of antiretroviral triple-drug therapy in a community-based cohort. *AIDS Res Hum Retroviruses* 1999;15:1631-8.
204. Pradier C, Carrieri P, Bentz L, et al. Impact of short-term adherence on virological and immunological success of HAART: a case study among French HIV-infected IDUs. *Int J STD AIDS* 2001;12:324-8.
205. Safren SA, Otto MW, Worth JL, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behav Res Ther* 2001;39:1151-62.
206. Tsasis P. Adherence assessment to highly active antiretroviral therapy. *AIDS Patient Care STDS* 2001;15:109-15.
207. Van Wijngaerden E, De Saar V, De Graeve V, et al. Nonadherence to highly active antiretroviral therapy: clinically relevant patient categorization based on electronic event monitoring. *AIDS Res Hum Retroviruses* 2002;18:327-30.
208. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* 2002;16:269-77.
209. Williams A. Antiretroviral therapy: factors associated with adherence. *J Assoc Nurses AIDS Care* 1997;8(Suppl):18-23.
210. Wagner JH, Justice AC, Chesney M, Sinclair G, Weissman S, Rodriguez-Barradas M. Patient- and provider-reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. *J Clin Epidemiol* 2001;54(Suppl 1):S91-8.
211. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee and Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000;12:255-66.
212. Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001;358:1322-7.
213. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis* 2002;34:838-46.
214. Gerard Y, Maulin L, Yazdanpanah Y, et al. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. *AIDS* 2000;14:2723-30.
215. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000;356:1423-30.

216. Kessler HA, Johnson J, Follansbee S, et al. Abacavir expanded access program for adult patients infected with human immunodeficiency virus type 1. *Clin Infect Dis* 2002;34:535-42.
217. Hervey PS, Perry CM. Abacavir: a review of its clinical potential in patients with HIV infection. *Drugs* 2000;60:447-79.
218. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002;359:727-32.
219. Perry CM, Noble S. Didanosine: an updated review of its use in HIV infection. *Drugs* 1999;58:1099-135.
220. Hurst M, Noble S. Stavudine: an update of its use in the treatment of HIV infection. *Drugs* 1999;58:919-49.
221. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. *AIDS* 1999;13:1659-67.
222. Reisler K. High hepatotoxicity rate seen among HAART patients. *Aids Alert* 2001;16:118-9.
223. Murphy R, Montaner J. Nevirapine: a review of its development, pharmacological profile and potential for clinical use. *Exp Opin Invest Drugs* 1996;5:1183-9.
224. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis* 2001;32:124-9.
225. Wong KH, Chan KC, Lee SS. Sex differences in nevirapine rash. *Clin Infect Dis* 2001;33:2096-8.
226. Ho TT, Wong KH, Chan KC, Lee SS. High incidence of nevirapine-associated rash in HIV-infected Chinese. *AIDS* 1998;12:2082-3.
227. Nunez M, Lana R, Mendoza JL, Martin-Carbonero L, Soriano V. Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001;27:426-31.
228. Dietrich D, Stern J, Robinson P, Hall D, Carlier H. *Analyses of four key clinical variables to assess the risk of hepatotoxicity with nevirapine: correlation with CD4 levels, hepatitis B and C seropositivity, and baseline liver function tests.* 1st International AIDS Society Conference on HIV Pathogenesis and Treatment., Buenos Aires, Argentina, July 2001.
229. Bartlett J, Committee. *Severe liver toxicity in patients receiving two nucleoside analogues and a non-nucleoside reverse transcriptase inhibitor.* 8th Conference on Retroviruses and Opportunistic Infections., Chicago, IL, February 2001.
230. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001;15:1261-8.
231. Bourezane Y, Salard D, Hoen B, Vandel S, Drobacheff C, Laurent R. DRESS (drug rash with eosinophilia and systemic symptoms) syndrome associated with nevirapine therapy. *Clin Infect Dis* 1998;27:1321-2.
232. Gonzalez de Requena D, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. *AIDS* 2002;16:290-1.

233. Bonfanti P, Valsecchi L, Parazzini F, et al. Incidence of adverse reactions in HIV patients treated with protease inhibitors: a cohort study. Coordinamento Italiano Studio Allergia e Infezione da HIV (CISAI) Group. *J Acquir Immune Defic Syndr* 2000;23:236-45.
234. Yarasheski KE, Tebas P, Sigmund C, et al. Insulin resistance in HIV protease inhibitor-associated diabetes. *J Acquir Immune Defic Syndr* 1999;21:209-16.
235. Powderly WG. Long-term exposure to lifelong therapies. *J Acquir Immune Defic Syndr* 2002;29(Suppl 1):S28-40.
236. Stenzel MS, Carpenter CC. The management of the clinical complications of antiretroviral therapy. *Infect Dis Clin North Am* 2000;14:851-78, vi.
237. Shevitz A, Wanke CA, Falutz J, Kotler DP. Clinical perspectives on HIV-associated lipodystrophy syndrome: an update. *AIDS* 2001;15:1917-30.
238. Wanke CA, Falutz JM, Shevitz A, Phair JP, Kotler DP. Clinical evaluation and management of metabolic and morphologic abnormalities associated with human immunodeficiency virus. *Clin Infect Dis* 2002;34:248-59.
239. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. *Antimicrob Agents Chemother* 2000;44:3451-5.
240. Gisolf EH, Dreezen C, Danner SA, Weel JL, Weverling GJ. Risk factors for hepatotoxicity in HIV-1-infected patients receiving ritonavir and saquinavir with or without stavudine. Prometheus Study Group. *Clin Infect Dis* 2000;31:1234-9.
241. Scribner AN, Troia-Cancio PV, Cox BA, et al. Osteonecrosis in HIV: a case-control study. *J Acquir Immune Defic Syndr* 2000;25:19-25.
242. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000;14:F63-7.
243. Gaughan D, Mofenson L, Hughes M, et al. Osteonecrosis of the hip (Legg-Calve-Perthes disease) in HIV-infected children in long-term follow-up. Pediatric AIDS Clinical Trials Group (PACTG). 219. Vol. 2002: Pediatrics 2002: http://www.pediatrics.org/cgi/content/full/109/5/e74
244. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics* 1998;102:101-9.

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