World Health Organization

HIV/AIDS Programme
Strengthening health services to fight HIV/AIDS

ANTIRETROVIRAL THERAPY FOR HIV INFECTION IN ADULTS AND ADOLESCENTS:
Recommendations for a public health approach

2006 revision

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ACKNOWLEDGEMENTS

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ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
AB	antibody
ABC	abacavir
ACTG	AIDS Clinical Trials Group
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATS	amphetamine type stimulants
ATV	atazanavir
AUC	area under curve
AZT	zidovudine (also known as ZDV)
b.d.	twice daily
BMI	body mass index
CD4 count	CD4+ T-cell (T-lymphocyte bearing CD4 receptor)
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTX	co-trimoxazole
CXR	chest X-ray
d4T	stavudine
DART	Development of Antiretroviral Therapy (in Africa)
DBS	dried blood spot
ddI	didanosine
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EC	enteric-coated
EFV	efavirenz
EIA	enzyme immunoassay
EPTB	extrapulmonary tuberculosis
FBC	full blood count
FDA	Food and Drug Administration (USA)
FDC	fixed-dose combination
FPV	fos-amprenavir
FTC	emtricitabine
GDG	Guidelines Development Group
GI	gastrointestinal
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
hgc	hard gel capsule
HIV	human immunodeficiency virus
HIVDR	HIV drug resistance
HIVNET	HIV Network for Prevention Trials
HIVResNet	Global HIV Drug Resistance Network
HSV	herpes simplex virus
IDU	injecting drug user
IDV	indinavir
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LDH	lactic dehydrogenase
LPV	lopinavir
MTCT	mother-to-child transmission (of HIV)
NAM	nucleoside/nucleotide analogue mutation
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHL	oral hairy leukoplakia
OI	opportunistic infection
OST	opioid substitution treatment
PCP	Pneumocystis pneumonia
PETRA	Perinatal Transmission Study
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
/r	low-dose ritonavir
RBV	ribavirin
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reverse transcriptase inhibitor
RTV	ritonavir
SJS	Stevens-Johnson syndrome
SQV	saquinavir
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TENS	toxic epidermal necrolysis
TLC	total lymphocyte count
VL	viral load
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
USA	United States of America
WBC	white blood cell count
WHO	World Health Organization

1. INTRODUCTION

By the end of 2005 the World Health Organization estimated that there were just over 1.3 million people receiving antiretroviral therapy (ART) in low-income and middle-income countries, representing 20% of the 6.5 million estimated to need it. Since the need to close the treatment gap was declared a global public health emergency, and the launch of the "3 by 5" initiative by WHO and UNAIDS in December 2003, the number of people receiving ART has more than tripled. Over the last year the number of people receiving ART globally has increased by about 300 000 every six months. Scale-up in Africa, the continent hardest hit by the HIV epidemic, has been most dramatic, rising from 100 000 at the end of 2003 to 810 000 by the end of 2005. ART treatment programmes in resource-poor settings have efficacy rates similar to those reported for developed countries.[1]

The landscape has also changed dramatically. ART is now considered an integral part of the comprehensive response to HIV prevention, care and support. Globally, the commitment has been made by the G8 group of nations to universal access to ART for all who need it and this was confirmed by the United Nations General Assembly (resolution A/60/l.43). It is hoped to achieve this by the end of 2010.

Much of this progress has been made since the revision of *Scaling up of antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach*, completed by the end of 2003 and published by WHO early in 2004. In that document, treatment options were consolidated into two sequential potent regimens termed first-line and second-line ART, and approaches to simplified clinical and immunological monitoring were outlined. A recent evaluation has noted that almost all high-burden countries have adopted or adapted the WHO treatment guidelines to frame national recommendations.[2] Consequently, almost all the 1.3 million people currently on ART are receiving WHO-recommended first-line regimens delivered in accordance with a public health approach. With a simple first-line adult formulary of ARVs the production of fixed-dose first-line combinations has been encouraged, and products are currently available from at least 23 producers. ARV prices for first-line regimens fell by between 35% and 53% from 2003 to 2005, particularly in low-income countries.

However, since 2003, considerable new evidence and programmatic experience have been gained, necessitating a further revision of the adult guidelines. This has been done in tandem with the revision of *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach*. Meanwhile, the section on paediatric therapy has been revised and is now separately produced as *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access; recommendations for a public health approach*.

The public health approach to the delivery of comprehensive HIV care remains the basis for all these ARV guidelines. The public health delivery of ART focuses on maximizing survival at the population level through standardized sequencing of the available ARVs, delivered to individuals by means of simplified approaches and supported by clinical and basic laboratory monitoring. It encompasses the guiding principles of chronic disease management with a strong focus on ART adherence and integrated, decentralized health care delivery linked to reduction of HIV transmission. Consideration is also given to the operational and programmatic requirements

necessary to achieve sustainable access to effective ART in resource-limited settings where individualized patient management by physicians specialized in HIV medicine is not feasible.

The basic concepts of the 2003 revision of the guidelines have been retained: a standardized formulary for first-line and second-line ART, with the use of two NRTIs and an NNRTI as the standard first-line approach; maintenance of the PI class as the mainstay of second-line regimens; and simplified patient management and standardized laboratory monitoring to indicate when to start, when to substitute for toxicity, and when to switch for failure or stop therapy (the "four Ss" of simplified clinical decision-making). WHO recognizes that, because access to basic laboratory services continues to be limited, many treatment decisions have to be based on clinical status alone. WHO continues to advocate wider access to monitoring tools, particularly CD4 testing, to guide the initiation and monitoring of ART. Clinical and immunological monitoring are supported by the recently finalized *Revised WHO clinical staging and immunological classification of HIV, and case definition of HIV for surveillance of HIV disease in adults and adolescents,* which includes presumptive and definitive criteria for classifying clinical events related to HIV and AIDS. Previously, staging was hierarchical and irreversible. With immune reconstitution and improvement of clinical status a new concept of staging on therapy (T-staging) to indicate when switching should occur is being developed.

Because the previous editions of these guidelines were used extensively as a reference source for many countries developing their own national guidelines, additional material has been included in the 2006 revision to facilitate the key role of the document as a reference tool. There are more detailed considerations on the use of ART in women, patients with TB/HIV coinfection and injecting drug users (IDUs), and new sections on HIV / viral hepatitis coinfection, on the failure of second-line therapy, and on future directions for improving access to care and treatment.

The ARVs recommended in the standard two NRTIs/NNRTI first-line approach have been reviewed and choices for first-line drugs have been broadened. Consideration is given to the long-term toxicities of stavudine, widely used in national programmes as the preferred NRTI to accompany lamivudine in first-line treatment for reasons of cost and availability. As a consequence of these long-term toxicities, e.g. lipoatrophy, stavudine is no longer included as a preferred drug for initial therapy in United States and European guidelines,[3][4] and WHO now recommends zidovudine as one of the preferred NRTI options to be considered by countries. Three new antiretrovirals (tenofovir, abacavir and emtricitabine) have been added as first-line ART options: tenofovir and abacavir were previously recommended for second-line ART; emtricitabine is regarded as an equivalent product to lamivudine. Tenofovir has been included because of its excellent safety profile and ease of use (once daily). Abacavir has been added as a first-line alternative in order to harmonize adult regimens and paediatric guidelines so as to facilitate a comprehensive family approach. WHO recognizes that price considerations for these drugs will remain central to the choices made in national programmes.

With these changes, a triple NRTI therapy regimen can be constructed to complement the standard two NRTIs/NNRTI first-line approach. The use of triple NRTI therapy may be considered as an alternative simplification approach in certain situations, such as cotreatment of tuberculosis

and HIV, NNRTI intolerance, coinfection with hepatitis B or C with hepatic dysfunction, in pregnant and non-pregnant women with CD4 counts between 250 and 350 cells/mm^3, and the treatment of HIV-2 infection. This approach simplifies toxicity and drug interaction management in first-line therapy and, importantly, preserves the PI class for use in second-line regimens. However, there is randomized clinical trial evidence that some triple NRTI combinations are less effective virologically than standard first-line therapy based on two NRTIs/NNRTI.

> *ART should be delivered as part of a package of care interventions, including the provision of co-trimoxazole prophylaxis, the management of opportunistic infections and comorbidities, nutritional support and palliative care.*

Second-line therapy remains based on the PI class, ideally supported by an NRTI backbone using two new (previously unused) agents to minimize cross-resistance; ritonavir-boosted PIs are recommended in order to enhance potency. PIs are reserved for second-line therapy. The use of PIs in a first-line regimen essentially rules out second-line options in the setting of limited formularies: no potent or durable options have been identified for recommendations in these guidelines following initial PI use and failure because of the limited formularies present in the public sector in resource-limited countries. The choice of new NRTIs for use following the failure of an initial two NRTIs/NNRTI-based regimen remains a challenge. The efficacy of NRTIs in a second-line regimen can be expected to be compromised by the inevitable accumulation of NRTI mutations when switching is based on clinical or immunological failure. Viral load testing may have a role in identifying failure and indicating when to switch in some patients, and WHO advocates wider access to virological testing in tertiary centres and new, simpler virological assays. WHO also strongly promotes the use of virological testing for the early definitive diagnosis of HIV infection in HIV-exposed infants, facilitated by the use of dried blood spots and centralized screening. However, it is not yet clear what viral load threshold best indicates failure when ART is only available in first-line or second-line regimens and there is only one switch. Given the continued cost and complexity of the current technology, viral load monitoring is still not suitable for wide use in the public health management of ART. However, it is likely that the situation will change when studies identify threshold viral load level(s) that define first-line failure, and when simpler technology, ideally at the point of care, can be developed and made available.

2. OBJECTIVES OF THE DOCUMENT

This publication is intended to serve as a reference tool for countries with limited resources as they develop or revise national guidelines for the use of ART in adults and postpubertal adolescents (see Annex 9 for pubertal Tanner staging; prepubertal adolescents should follow the WHO paediatric guidelines). The material presented takes updated evidence into account, including new ART treatment options, and draws on the experience of established ART scale-up programmes. The simplified approach, with evidence-based standards, continues to be the basis of WHO recommendations for the initiation and monitoring of ART. The guidelines are primarily intended for use by national and regional HIV programme managers, managers of nongovernmental organizations delivering HIV care services, and other policy-makers who are involved in the scaling up of comprehensive HIV care and ART in resource-limited countries. The comprehensive, up-to-date technical and clinical information on the use of ART, however, also makes these guidelines useful for clinicians in resource-limited settings. The recommendations contained in these guidelines are made on the basis of different levels of evidence from randomized clinical trials, high-quality scientific studies, observational cohort data and, where insufficient evidence is available, expert opinion. The strengths of the recommendations in Table 1 are intended to indicate the degrees to which the recommendations should be considered by regional and country programmes. Cost-effectiveness is not explicitly considered as part of the recommendations, although the realities of human resources, health system infrastructures and socioeconomic issues should be taken into account when the recommendations are being adapted to regional and country programmes.

Table 1. Grading of recommendations and levels of evidence

Strength of recommendation	Level of evidence to make for recommendation
A. Recommended – should be followed B. Consider – applicable in most situations C. Optional	I. At least one randomized controlled trial with clinical, laboratory or programmatic end-points II. At least one high-quality study or several adequate studies with clinical, laboratory or programmatic end-points III. Observational cohort data, one or more case-controlled or analytical studies adequately conducted IV. Expert opinion based on evaluation of other evidence

Adapted from:

1. The British HIV Association (BHIVA) treatment guidelines for 2005, http://www.bhiva.org/guidelines/2005/BHIVA-guidelines
2. Developing an evidence-based guide to community preventive services – methods. The Task Force on Community Preventive Services. *Am J Prev Med* 2000;18(1S):35-43.
3. WHO Evidence Network, http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050408-5
4. EBM-Guidelines, Evidence-based medicine, http://www.ebm-guidelines.com

3. DEVELOPMENT OF THE GUIDELINES

In June 2005, WHO convened a meeting of the Guidelines Development Group (GDG) to review existing ART recommendations for resource-limited settings. GDG was asked to review the 2003 guidelines in the light of new data and the considerable experience of scaling up ART programmes that had been gained in many countries. GDG recognized the continued need for simple evidence-based guidelines, for these to be revised, and for the revised recommendations to be harmonized with the ART guidelines for infants, children and prepubertal adolescents and with those for the use of ARVs in the prevention of mother-to-child-transmission (PMTCT).

The standardization and simplification of treatment and monitoring continues to be the prime consideration underpinning WHO recommendations for the use of ART, in order to widen access to effective therapy in resource-limited settings where individualized patient management by physicians specialized in HIV medicine is not feasible. Standardized clinical and, where available, immunological (CD4) evaluation to guide the initiation of ART, the use of appropriate formulations, including fixed- dose combinations (FDCs) of ARVs,[12] simple laboratory tools and a symptom-directed approach to monitoring adverse events, are keys to the simplified approach.

GDG reviewed the WHO 2003 ART guidelines and considered new evidence and treatment options with respect to:

- the initiation of ART;
- long-term toxicities of individual ARVs;
- preferred first-line and second-line regimens;
- reasons for substituting (toxicity) or switching (failure);
- the way in which treatment should be monitored.

The review suggested that the following areas should be revised and better elaborated in the 2005−2006 guidelines:

- second-line options;
- special considerations on ART with major coinfections (TB, viral hepatitis), for injecting drug users and in pregnancy;
- specific considerations on side-effects of ART and on drug adherence;
- salvage strategies.

GDG recognized that while the guidelines were intended primarily to provide a technical basis for the scale-up of ART programmes at the national level, the recommendations, supported by evidence and experience, were a powerful tool in advocating greater access to ART and could create incentives to increase the production and reduce the cost of ARV drugs and laboratory diagnostics (including CD4 and viral load testing). It was also necessary for the guidelines to highlight the importance of preventing HIV secondary transmission and to emphasize that expanding access to ART offered opportunities to enhance prevention efforts.

In addition to the technical recommendations on the use of ART, GDG considered that the following key recommendations should be included in the revised guidelines.

- Wider availability of appropriate and affordable CD4 testing and plasma viral load testing should be advocated in order to guide decision-making on when to switch ART regimens in resource-limited settings.

- Free ART at the point of delivery or greatly reduced prices of ART to HIV-infected people should continue to be advocated

- Targeted efforts to ensure access for vulnerable populations should be supported.

GDG also recognized that the field of HIV therapy was rapidly evolving and that new evidence and major advances were being regularly reported. Further revisions and updating of the guidelines were therefore inevitable. In the interim a subgroup would continue to review new data and evidence and would post relevant updates and recommendations on the WHO web site.

4. WHEN TO START ANTIRETROVIRAL THERAPY IN ADULTS AND ADOLESCENTS

In resource-limited settings the decision to initiate ART in adults and adolescents relies on clinical and immunological assessment. In order to facilitate the rapid scale-up of ART programmes with a view to achieving universal access to this therapy, WHO emphasizes the importance of using clinical parameters in deciding when to initiate it. However, it is recognized that the value of clinical staging in deciding when to initiate and monitor ART is improved by additional information on baseline and subsequent (longitudinal) CD4 cell counts. While WHO continues to advocate wider availability of affordable point-of-care CD4 cell count testing, the lack of a CD4 count should not delay the initiation of ART if the patient in question is clinically eligible. WHO encourages national programmes to increase access to CD4 measurement technologies.

The process of initiating ART involves assessing patient readiness to commence therapy and an understanding of its implications (lifelong therapy, adherence, toxicities). Access to nutritional and psychosocial support and to family and peer support groups is important when decisions are being made about the initiation of ART.

4.1. Clinical assessment of HIV-infected adults and adolescents

The WHO classification of HIV-associated clinical disease has recently been revised in order to provide greater consistency between the adult and paediatric classification systems (Table 2).

Table 2. WHO classification of HIV-associated clinical disease[a]

Classification of HIV-associated clinical disease	WHO clinical stage
Asymptomatic	1
Mild	2
Advanced	3
Severe	4

a   See Annexes 1 and 2 for further details.

Clinical staging is intended for use where HIV infection has been confirmed by HIV antibody testing. It should form part of the baseline assessment (first visit) on entry into a care and treatment programme and is used to guide decisions on when to start co-trimoxazole prophylaxis and when to start and switch ART in situations where CD4 testing is not available. Annexes 1 and 2 provide further details of the specific staging events and the criteria for recognizing them.

ART results in improvement in clinical status and brings about effective reversal of the clinical stage in patients with symptomatic disease. However, the value of clinical staging in monitoring the efficacy of ART, defining ART failure and determining when to switch ART is less clear. Studies are urgently needed to address the use of clinical criteria (clinical stage on treatment) in deciding when to switch ART in the absence of CD4 cell counts or viral load testing.

4.2. Immunological assessment of HIV-infected adults and adolescents

The optimum time to commence ART is before patients become unwell or present with their first opportunistic infection. Immunological monitoring (CD4 testing) is the ideal way to approach this situation. A baseline CD4 cell count not only guides the decision on when to initiate ART but is also essential if CD4 counts are to be used to monitor ART. Table 3 summarizes the immunological criteria for the initiation of ART.

Table 3. CD4 criteria for the initiation of ART in adults and adolescents

CD4 (cells/mm³) [a]	Treatment recommendation [b]
<200	Treat irrespective of clinical stage [c] **[A-III]**
200−350	Consider treatment and initiate before CD4 count drops below 200 cells/mm³ [c d e] **[A-III]**
>350	Do not initiate treatment **[A-III]**

a   CD4 cell count should be measured after stabilization of any intercurrent condition.

b   CD4 cell count supplements clinical assessment and should therefore be used in combination with clinical staging in decision-making.

c   A drop in the CD4 cell count below 200 cells/mm³ is associated with a significant increase in opportunistic infections and death.

d   The initiation of ART is recommended for all patients with any WHO clinical stage 4 disease and some WHO clinical stage 3 conditions, notably pulmonary TB (see Section 12.1) and severe bacterial infections.

e   The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 <350 cells/mm³ (see Section 11.2).

The benchmark threshold marking a substantially increased risk of clinical disease progression is a CD4 cell count of 200 cells/mm³. Although it is never too late to initiate ART, patients should preferably begin the therapy before the CD4 cell count drops to or below 200 cells/mm³ **[A-III]**. The optimum time to initiate ART with a CD4 cell count of 200−350 cells/mm³ is unknown. Patients with CD4 cell counts in this range require regular clinical and immunological evaluation.

The treatment of patients with WHO clinical stage 4 disease should not depend on a CD4 cell count determination: all such patients should initiate ART **[A-III]**. For WHO clinical stage 3 conditions, a threshold of 350 cells/mm³ has been identified as a level below which functional immune deficiency is present and ART should be considered. This level also conforms to what is indicated in other consensus guideline documents.[3 4] CD4 cell counts can be helpful in categorizing patients with stage 3 conditions in respect of their need for immediate therapy. For example, pulmonary tuberculosis or severe bacterial infections can occur at any CD4 count level and it is reasonable to delay ART and continue to monitor patients with CD4 cell counts above 350 cells/mm³. However, the initiation of ART is recommended for all HIV-infected individuals with pulmonary TB and CD4 counts below 350 cells/mm³ (see Section 12.1) and also for patients with severe bacterial infections who have CD4 counts below this value. It is also recommended

that all pregnant women with any stage 3 disease and CD4 counts below 350 cells/mm³ initiate ART (see Section 11.2.1). For patients with clinical stage 1 or 2 disease, a CD4 count below 200 cells/mm³ is a clear indication for treatment **[A-III]**. Although there are no randomized trial data on the CD4 cell count level at which to start therapy in asymptomatic persons, data from a number of cohorts have been consistent in demonstrating that disease progression is greater in persons who start antiretroviral therapy with CD4 counts below 200 cells/mm³ than in those starting therapy above this level.[5 6 7 8 9 10] In general these studies have not been able to detect a difference in outcome between persons who start therapy at CD4 counts of 200−350 cells/mm³ and those who do so at CD4 counts above 350 cells/mm³. However, if the CD4 count is above 350 cells/mm³, ART should be delayed.

Absolute CD4 cell counts fluctuate within individuals and can vary with intercurrent illness. If possible, CD4 testing should be repeated if a major management decision rests on the value. Serial measurements remain more informative than individual values because they reflect trends over time, including the response to therapy.

In the absence of a CD4 cell count, a total lymphocyte count (TLC) below 1200 cells/mm³ in patients with symptomatic HIV disease has been recommended as a guide to the initiation of ART. While the TLC correlates relatively poorly with the CD4 cell count in asymptomatic persons, in combination with clinical staging it has been reported as a useful marker of prognosis and survival.

It has not been possible to translate the predictive ability of TLC into a specific TLC threshold for determining treatment eligibility. Data suggest that a TLC below 1200 cells/mm³ as a surrogate for a CD4 count below 200 cells/mm³ has high positive predictive value but poor negative predictive value and that it cannot be used alone in asymptomatic patients to determine treatment eligibility. For the purpose of determining when to start treatment a single TLC threshold cannot be recommended. It remains a useful predictive marker of disease progression. The TLC is thus only useful in deciding when to initiate ART in symptomatic patients with WHO clinical stage 2 disease. It is not useful and is not recommended for monitoring the response to ART or for deciding whether ART is failing.

The TLC should be measured with an automated reader as manual counts are too inaccurate (especially in the presence of lymphopenia) and are too time-consuming for routine use. Many countries with automated machines also have CD4 (bench top) measurement technology available.

In general, ART programmes have not adopted the TLC as a trigger for initiating ART. Because of the uncertainties surrounding the use of the TLC and its relatively infrequent use, WHO considers that it should be gradually eliminated from the adult ARV guidelines. Better data exist for the relationship of the TLC and HIV disease in children, and the current paediatric guidelines continue to employ TLC thresholds for consideration of therapy when CD4 assays are not available. Table 4 summarizes the recommendations for initiating ART in accordance with clinical stages and the availability of immunological markers.

Table 4. Recommendations for initiating ART in adults and adolescents in accordance with clinical stages and the availability of immunological markers

WHO clinical staging	CD4 testing not available	CD4 testing available
1	Do not treat **[A-III]**	Treat if CD4 count is below 200 cells/mm^3 [a] **[A-III]**
2	Do not treat [b] **[B-III]**	
3	Treat **[A-III]**	Consider treatment if CD4 count is below 350 cells/mm^3 [a c d] and initiate ART before CD4 count drops below 200 cells/mm^3 [e] **[B-III]**
4	Treat **[A-III]**	Treat irrespective of CD4 cell count **[A-III]**

a   CD4 cell count advisable to assist with determining need for immediate therapy for situations such as pulmonary TB and severe bacterial infections, which may occur at any CD4 level.

b   A total lymphocyte count of 1200/mm^3 or less can be substituted for the CD4 count when the latter is unavailable and mild HIV disease exists. It is not useful in asymptomatic patients. Thus, in the absence of CD4 cell counts and TLCs, patients with WHO adult clinical stage 2 should not be treated.

c   The initiation of ART is recommended in all HIV-infected pregnant women with WHO clinical stage 3 disease and CD4 counts below 350 cells/mm^3 (see Section 11.2).

d   The initiation of ART is recommended for all HIV-infected patients with CD4 counts below 350 cells/mm^3 and pulmonary TB (see Section 12.1) or severe bacterial infection.

e   The precise CD4 cell level above 200/mm^3 at which ARV treatment should be started has not been established.

4.3.   Virological assessment of HIV-infected adults and adolescents

Plasma viral load measurement is not necessary before initiating ART. It rarely informs the clinical decision as to when ART should begin if both CD4 testing and the assessment of clinical staging are performed. From the public health perspective, the expanded access to viral load determination should be considered primarily for the definitive diagnosis of HIV infection in infants and children aged under 18 months. It is hoped that more affordable methods of determining viral load, ideally at the point of care, will become available to improve the standard of monitoring for patients on ART, especially in situations where ART switching is being considered.

5. WHAT TO START: RECOMMENDED FIRST-LINE ARV REGIMENS

5.1. Considerations for treatment on the basis of a public health approach

The public health approach to ART scale-up in resource-limited settings aims to support the development of treatment programmes that can reach as many people as possible. Countries are encouraged to use the public health approach to support and facilitate wider access to ART. Among the key tenets of this approach are the standardization and simplification of ARV regimens. In the 2003 edition of these guidelines [11] it was suggested that countries select a first-line regimen and a limited number of second-line regimens, recognizing that individuals who cannot tolerate or fail the first-line and second-line regimens may require input from more experienced clinicians. The use of standardized regimens has been an essential factor in expanding access to ART and has facilitated WHO's efforts to assist Member States in trying to achieve this goal. The use of such regimens remains the essential approach to ARV regimen selection adopted in this version of the guidelines, although the recommendations for the selection of first-line and second-line regimens have been revised. When a treatment plan is being designed it is important to maximize the durability and efficacy of any first-line regimen by incorporating approaches that support adherence.

When selecting appropriate ARV regimens, the following factors at the programme level should be taken into consideration:

- suitability of the drug formulation, especially the availability of fixed-dose combinations (see Annex 10);

- licensing approval by national drug regulatory authorities for the product and recommended dose;

- toxicity profile;

- laboratory monitoring requirements;

- potential for maintenance of future treatment options (sequencing of ARVs);

- promotion of adherence (ARVs with once-daily or twice-daily dosing);

- prevalent coexistent conditions (TB and hepatitis B);

- special considerations for women of childbearing potential or who are pregnant;

- availability from local and international manufacturers, including procurement and supply chain logistics;

- price[1] and cost-effectiveness;

- specific ARV requirements for HIV-2 infections that are naturally resistant to NNRTIs.

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1   For most updated information on ARVs available for resource-limited settings, consult the last edition of Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS, published by UNICEF/UNAIDS/WHO/ MSF and available at: http://www.who.int/medicines/areas/access/med_prices_hiv_aids/en/

The expanded number of options in the updated first-line treatment regimen recommendations does not necessarily place increased demands on country formularies with respect to the number of drugs to be stocked. WHO advises that country and programme managers should review these recommendations and answer the following questions.

- What is the appropriate primary first-line regimen for the population?

- What drugs should be readily available for drug substitutions for intolerance, toxicity or special circumstances such as pregnancy and active tuberculosis?

- What will be reserved for the second-line NRTI backbone?

In responding to these questions, a limited drug formulary for first-line therapy can still be pursued in order to keep programmes as streamlined as possible. For programmes that propose to revise their regimens a period of increased formulary complexity may exist during the transition. WHO offers the following suggestions for programmes wishing to start or maintain an ARV rollout with an NNRTI-based regimen.

- Choose NVP *or* EFV as the primary NNRTI; both should be available for mutual substitution for toxicity and for issues related to drug choice in pregnancy and TB.

- Choose either 3TC *or* FTC. It is not necessary to stock both.

- Choose one companion NRTI to combine with 3TC or FTC in order to construct the two NRTIs component of the regimen, *and* an alternative for substitution.

5.2. Constructing the first-line regimen

GDG continues to recommend that the first-line regimen for adults and adolescents contain two NRTIs plus one NNRTI (Fig. 1). This recommendation is based on available evidence, clinical experience and programmatic feasibility for the wider introduction of ART in resource-limited settings **[A-I]**. Regimens based on combination of two NRTIs plus one NNRTI are efficacious, are generally less expensive than other regimens, have generic formulations,[12] are often available as FDCs and do not require a cold chain. In addition, they preserve a potent new class (protease inhibitors) for second-line treatments. Disadvantages include different drug half-lives which complicate ART stopping procedures, the fact that a single mutation is associated with resistance to some drugs (3TC and the NNRTIs), and cross-resistance within the NNRTI class.

The thiacytadine analogues (3TC or FTC) are pivotal to first-line regimens. 3TC or FTC should be used with a companion nucleoside or nucleotide analogue, the choices here being AZT, TDF, ABC or d4T.

The preferred NRTI backbone is composed of AZT or TDF combined with either 3TC or FTC **[A-I]**. Didanosine (ddI) is an adenosine analogue NRTI recommended to be reserved for second-line regimens (see Section 10.2). Finally an NNRTI, either EFV or NVP, should be added **[A-I]**.

WHO recommends that countries purchase and stock a higher proportion of the preferred NRTI and NNRTI and a smaller amount of the drug that will be used in case of toxicity and/or contraindication of the first choice. This means procuring two NRTIs and two NNRTIs in addition to 3TC/FTC. For example, TDF can be a substitute for AZT in patients with severe AZT-induced anaemia, and EFV can be a substitute for NVP in cases of NVP-associated hepatotoxicity.

A triple NRTI regimen should be considered as an alternative for first-line ART in situations where NNRTI options provide additional complications and to preserve the PI class for second- line treatment **[C-I]** (e.g. in women with CD4 counts of 250−350 cells/mm^3; coinfection with viral hepatitis or tuberculosis; severe adverse reactions to NVP or EFV, infection with HIV-2). Recommended triple NRTI combinations are zidovudine + lamivudine + abacavir **[A-I]** and zidovudine + lamivudine + tenofovir **[A-II]** (See Fig. 1).

Fig. 1. First-line ARV drugs for adults and adolescents
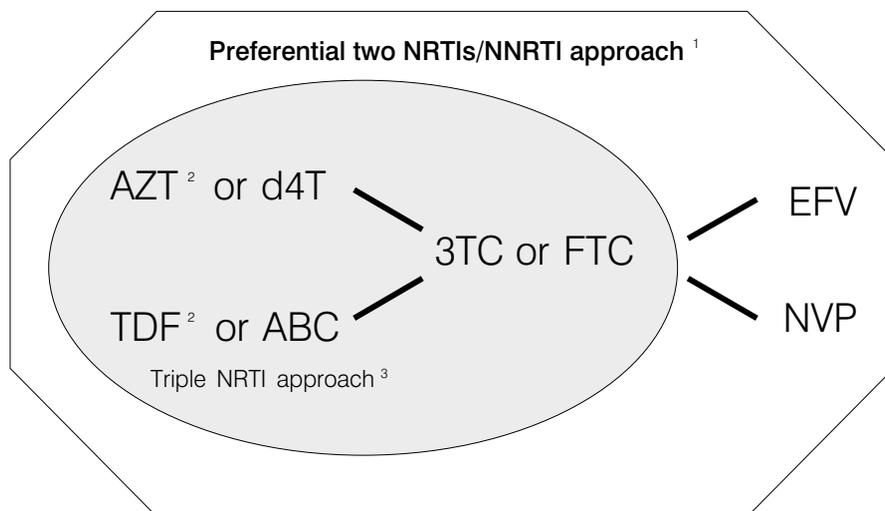
1   Preferential two NRTIs/NNRTI approach is based upon a combination of three drugs: two NRTIs combined with either NVP or EFV as the NNRTI.
2   Preferred NRTI to be combined with 3TC or FTC in standard first-line regimens.
3   Triple NRTI approach (i.e. three NRTI drugs selected only from the options shown within the dotted circle) can be considered as an alternative for first-line regimens in situations where NNRTI options provide additional complications (e.g. women who have CD4 counts between 250 and 350 cells/mm^3, viral hepatitis coinfection, TB coinfection, severe reactions to NVP or EFV, and HIV-2 infection) as discussed above.

Despite the expanded recommendations for TDF and ABC use in first-line regimens, many countries may prefer to continue maintaining these two NRTI options in second-line regimens. Regardless of whether they are used as first-line or second-line therapy, it is very important to include these two drugs in all national ARV formularies.

5.3. Notes on ARV combinations to be avoided or used with caution

Monotherapy or dual therapy should not be used to treat chronic HIV infection; they may only be used in the setting of PMTCT and post-exposure prophylaxis. Certain dual NRTI backbone combinations should not be used within three-drug therapy. These are d4T + AZT (proven antagonism), d4T + ddI (overlapping toxicities) and 3TC + FTC (interchangeable, but should not be used together). The combinations of TDF + 3TC + ABC and TDF + 3TC + ddI select for the K65R mutation and are associated with high incidences of early virological failure. The combinations of TDF + ddI + any NNRTI are also associated with high rates of early virological failure. However, the use of ddI should be reserved for second-line treatment, in which situation it is possible to consider TDF + ddI with boosted PIs, provided that caution and close monitoring are practised, until more data become available **[B-IV]**. The ddI dose should be adjusted when used concomitantly with TDF in order to reduce the toxicity risk (see footnote in Annex 3).

5.4. Choice of NRTIs

Lamivudine (3TC) has been and remains pivotal to all first-line ARV regimens in resource- limited settings. It is a core component of the dual NRTI backbone in all ARV combinations. It has proved safe, has a favourable toxicity profile, is nonteratogenic, is effective against hepatitis B infection, is relatively cheap to produce and is widely available, including in fixed- dose combinations (FDCs).

Emtricitabine (FTC) is a new NRTI that has recently been included in WHO's recommended first-line regimens. FTC is an equivalent alternative to 3TC as it is structurally related to 3TC, shares the same efficacy against HIV and hepatitis B virus and has the same resistance profile.[13] It is available as an FDC with TDF and, recently, a formulation with TDF, and EFV as a single, "three-in-one" pill was approved for clinical use. FTC is not yet on the WHO list of essential medications.

Zidovudine (AZT) is included as a preferred first-line NRTI. It is generally well tolerated and widely available in some FDCs (see Annex 10). Initial drug-related side-effects are headache and nausea, and it can also cause severe anaemia and neutropenia. Haemoglobin monitoring is recommended before and during treatment with AZT. This is particularly important in areas with a high prevalence of malaria, where anaemia is common. AZT is associated with metabolic complications, such as lactic acidosis and lipoatrophy, but to a lesser extent than d4T.

Tenofovir (TDF) is now included as a preferred first-line NRTI, because of its efficacy, ease of use and safety profile. This is a change from the 2003 guidelines, which recommended reserving the use of TDF as part of second-line regimens. TDF has a long intracellular half-life and can be used as part of once-daily regimens. It is generally well tolerated and studies suggest that it is not more frequently associated with renal dysfunction than other antiretroviral drugs.[14] [15] Despite some reports of renal insufficiency in patients receiving TDF, the occurrence of renal dysfunction in this context is usually attributable to other causes. The dose of TDF should be reduced in patients with underlying renal insufficiency. Because of limited data and concerns about potential

effects on fetal bone, some experts consider that TDF should be used in pregnant women only after careful consideration of other alternatives. The availability of TDF in resource-limited settings is currently limited but it is hoped that this drug will be become more widely available at affordable cost.

Abacavir (ABC) has been included in these revised guidelines as an alternative NRTI in first-line therapy. This is a change from the 2003 guidelines, in which reserving the use of ABC as part of second-line regimens was recommended. NRTI combinations containing ABC provide an effective NRTI backbone for use with NNRTIs or as part of a triple nucleoside regimen. Of all the NRTI drugs, ABC has the least effect on mitochondrial DNA depletion (associated with lipoatrophy, peripheral neuropathy and lactic acidosis) and is one of the possible substitutes for d4T or AZT in patients who develop lactic acidosis while receiving a regimen containing d4T or AZT. ABC can also be substituted for AZT in the event of intolerance. However, ABC is associated with a severe hypersensitivity reaction in approximately 2−5% of patients who receive the drug. The accurate determination of rates of ABC hypersensitivity in resource-constrained settings is an important clinical research objective.

Two of the reasons for including ABC in first-line recommendations for adults in these guidelines are: 1) clinical trial results in naive patients have demonstrated efficacy; 2) it is one of the few drugs available in a paediatric formulation. Thus, programme managers who wish to deliver family-based care to HIV-infected parents and children may find ABC/3TC an attractive dual NRTI component option to pursue if it can be made affordable. Despite being registered in many developing countries, its availability is currently limited by high cost.

Stavudine (d4T) is recognized as a life-saving drug that has played a crucial role in ART rollout, especially because of its availability in fixed-dose combinations (see Annex 10), the low cost of these FDCs and the clinical efficacy of the regimens recommended. d4T has also been preferred over AZT because of the requirement for limited or no laboratory monitoring. However, d4T has been consistently the NRTI most associated with lactic acidosis, lipoatrophy and peripheral neuropathy.[16] The latter toxicities are cumulative and often irreversible, and have the potential to affect adherence in the long term. The stigmatization associated with lipoatrophy can result in withdrawal from or refusal to enrol in ART programmes. Programmes that are dependent on d4T-based regimens may need to follow through with their current strategies so that needed treatment for individuals is not delayed. Because of the current wide availability in FDCs and considerably lower prices, d4T-containg regimens may still remain the most accessible option for people in urgent need of treatment in resource-limited settings in the short to medium term. At the same time, WHO notes that it is important to begin planning to move away from d4T-containing regimens so as to avoid or minimize the predictable toxicities associated with this drug. This recommendation is in agreement with other treatment guidelines, e.g. those published by the United States Department of Health and Human Services (DHHS) and the British HIV Association (BHIVA).

In the transition to safer first-line ARV choices, enhanced and closer monitoring for short-term and long-term d4T toxicities is recommended. This includes the training of health care workers and adequately informing patients of the signs and symptoms of lactic acidosis, lipoatrophy and peripheral neuropathy. Early recognition of d4T side-effects and switching to an alternative NRTI

(such as AZT, TDF or ABC) may reduce the severity of these drug toxicities. d4T may be used as a substitute for AZT if intolerance occurs and TDF and ABC are unavailable.

The role of dose reduction in mitigating d4T toxicity is uncertain. Because of the nature of the mitochondrial damage (cumulative toxicity), dose reduction may not prevent the occurrence of side-effects, and can at best delay the onset of symptoms. Some data suggest that dose reduction may be associated with a lower incidence of adverse events without compromising virological control.[17] However, dose reduction to 30 mg twice daily irrespective of weight can be a strategy to consider in the absence of alternatives (see Section 7.2).

5.5. Choice of NNRTIs

NNRTIs are potent and the key ARV class to be combined with a dual NRTI backbone in first-line therapy and facilitate the construction of relatively simple initial regimens. The NNRTIs efavirenz (EFV) and nevirapine (NVP) both have demonstrated clinical efficacy when administered in appropriate combination regimens. However, differences in toxicity profile, the potential for interaction with other treatments, and cost have to be considered when an NNRTI is being chosen.[18] [19] It is also necessary to take into account the inactivity of NNRTIs against HIV-2 infection and the fact that a single mutation can confer NNRTI class-wide drug resistance in HIV-1.

Nevirapine (NVP) is widely available (including in several FDCs) and is less costly than EFV. Moreover, significant experience has been gained with this drug at country level in resource-limited settings. However, a higher incidence of rash is associated with it than with EFV.[18] NVP-related rash may be severe and life-threatening, and Stevens-Johnson syndrome may occur. NVP is also associated with a rare but potentially life-threatening risk of hepatotoxicity. This makes the drug less suitable for treating patients who use other hepatotoxic medications. The initiation of NVP at the same time as other new drugs that can also cause rash (e.g. co-trimoxazole) should be avoided where possible. In the case of severe hepatic or skin reactions, NVP should be permanently discontinued and not restarted (see Section 8). NVP is the preferred NNRTI for women if there is potential for pregnancy or during the first trimester of pregnancy, when EFV cannot be used because of its teratogenic effect. However, symptomatic NVP-associated hepatic toxicity or serious rash, while uncommon, is more frequent in women than in men, and more likely to be seen in antiretroviral-naive women with higher CD4 cell counts (above 250 cells/mm^3). Thus, NVP should be used with caution in women with CD4 counts between 250 and 350 cells/mm^3. If it is used, careful monitoring is needed during the first 12 weeks of therapy (see Section 11.2.3). Annex 3 provides more detailed information on dosing and preparations of the above-listed drugs.

Efavirenz (EFV) can be used once daily and is generally well tolerated. However, it is relatively costly and currently less widely available than NVP. It is primarily associated with toxicities related to the central nervous system (CNS), teratogenicity and rash. Rash is generally mild, self-resolving and usually does not require the discontinuation of therapy. The CNS symptoms typically abate after two to four weeks in the majority of patients. EFV should be avoided in patients with a history of severe psychiatric illness, when there is a potential for pregnancy (unless effective contraception can be assured) and during the first trimester of pregnancy. In

these situations, NVP may be the better choice. EFV is the NNRTI of choice in individuals with TB/HIV coinfection who are receiving rifampicin-based TB therapy (see Section 12).

5.6. Triple NRTI-based regimens

The 2003 revision of these guidelines attempted to place triple NRTI-based regimens in perspective for resource-limited settings. A single study noted inferior virological efficacy (21% vs 10% virological failure rates for AZT + 3TC + ABC triple NRTI vs EFV-based ART regimen at 32 weeks) but comparative immunological efficacy of AZT + 3TC + ABC was reported vs AZT + 3TC + EFV or AZT + 3TC + ABC + EFV in AIDS Clinical Trials Group (ACTG) Study A5095.[20] These findings led to the recommendation that this triple NRTI regimen be moved to alternative tier status for initial therapy. This was consonant with consensus recommendations in industrialized countries at the time and had little impact on ARV rollout programmes in the developing world because of the cost of ABC and the AZT + 3TC + ABC fixed-dose combination. It was recommended that AZT + 3TC + ABC should remain a consideration in the setting of intolerance or resistance to NNRTIs when PI-based regimens were unavailable, and that second-line options should be preserved for the treatment of HIV-2 infection and of HIV/TB coinfected individuals when the treatment of both conditions simultaneously was indicated.

Important new data have emerged from the DART Trial, which used a TDF-based triple NRTI regimen[21]. In the DART virology substudy, of 300 persons who were treated with AZT + 3TC + TDF, 65% and 55% exhibited plasma HIV-1 RNA levels below 400 and 50 copies/ml respectively at 48 weeks of follow-up. These results should be interpreted with caution, given the lack of a control group and because, in other studies, EFV-containing regimens have achieved higher virological suppression rates. However, the DART results suggest the possibility that this regimen may have a useful role in first-line treatment.

Clearly, each triple NRTI regimen should be evaluated individually. While AZT + 3TC + ABC and AZT + 3TC + TDF have virological response rates that remain within an acceptable standard-of-care range, other triple NRTI regimens (e.g. 3TC + ABC + TDF and 3TC + ddI + TDF) have unacceptably high virological failure rates and high incidences of the K65R mutation,[22] [23] which confers cross-resistance to non-AZT nucleoside analogues. These regimens should not be used.

5.7. Use of protease inhibitors in initial therapy

It is recommended that PIs be reserved for second-line therapy because their use in an initial treatment regimen essentially rules out second-line options in the setting of limited formularies within a public health approach: no potent or durable regimens have been identified for recommendation following initial PI failure in this situation. With this important caveat, PIs as initial therapy with a standard dual NRTI backbone are an option for the treatment of viral types with intrinsic resistance to NNRTIs (e.g. HIV-2), for women with CD4 counts of 250−350 cells/mm^3, or for individuals for whom NNRTI drugs are severely toxic and triple NRTI therapy is not available or deemed inappropriate.

PIs are described in more detail in Section 10.

6. WHAT TO EXPECT IN THE FIRST SIX MONTHS OF THERAPY

The first six months on ART are critical. Clinical and immunological improvement should manifest themselves but are not always apparent and drug toxicities may emerge. Some patients fail to respond as expected or may even exhibit clinical deterioration initially. These issues combine to present specific challenges for simplified clinical management. Complications in the first few weeks following the initiation of ART are seen most commonly when therapy is started in patients with severe immunodeficiency. The apparent failure of a patient with advanced HIV disease to improve initially does not necessarily reflect a poor response to ART. It takes time for HIV viral replication to be controlled by ART and for the patient's immune system to strengthen. It also takes time for reversal of the catabolism associated with HIV infection, particularly in patients with significant HIV-associated wasting. Additionally, as a patient with advanced disease recovers immune function, exacerbation of previously subclinical coexisting infections (e.g. tuberculosis) may occur, resulting in an apparent worsening of disease. This is not attributable to failure of the therapy but to its success and the resulting immune reconstitution (see Section 6.4). Such symptoms might be interpreted as an initially poor response to ART. It is important to allow sufficient time on therapy before judging effectiveness and to consider the possibility of the immune reconstitution inflammatory syndrome (IRIS) in patients with worsening disease in the first few months of ART. In such cases, the switching of ART would be inappropriate.

6.1. CD4 recovery

In most patients, CD4 cell counts rise with the initiation of therapy and immune recovery. This may continue for many years into effective therapy, although this may be blunted if the baseline CD4 count is very low. However, even patients with CD4 counts below 10 cells/mm^3 can achieve an effective CD4 recovery, given sufficient time after the initiation of ART. Some patients may never have CD4 counts that exceed 200 cells/mm^3 and thus never leave the zone of severe immunosuppression. In those who achieve a substantial peak response, a subsequent progressive decline in CD4 counts in the absence of intercurrent illness indicates immunological failure. The baseline CD4 count and the trend of the CD4 response assessed by regular six-monthly CD4 counts are needed to best characterize and define immunological failure (see Section 8). In a minority of patients with advanced disease and low CD4 counts when therapy is initiated, the CD4 counts may not rise or may fall slightly, even with clinical improvement.

6.2. Early ARV toxicity

First-line drug toxicities fall into two categories: early, usually presenting in the first few weeks to months of therapy, and later (see Section 7). Common early and potentially severe toxicities are hypersensitivity to NNRTIs (EFV and NVP), normally occurring within the first few weeks of therapy, and AZT-related anaemia and neutropenia, typically presenting in the first few months of therapy. Many of the acute toxicities, if not identified early, can evolve into life-threatening and fatal events. Some of the higher mortality seen in the first six months of ART undoubtedly relates to drug toxicity. Currently, limited pharmacovigilance data are available for assessing the exact impact of ART toxicity on early mortality.

Some drug toxicities, especially hepatic and renal toxicity and lactic acidosis, may not be identified early if access to laboratory monitoring is limited. Hypersensitivity reactions may be difficult to distinguish from acute clinical events such as malaria and viral hepatitis and from the many manifestations of IRIS, which can present in the first few months on ART. Morbidity has been best quantified for anaemia related to AZT. The incidence of severe grade 4 anaemia (Hb <6.5 g/dl) peaks at about 2% in the first three months of therapy.[24][25] Section 7 details more specifically the clinical identification and management of toxicity.

6.3. Mortality on ART

While ART significantly decreases mortality, the latter is higher in the first six months than during the subsequent time on therapy, particularly when patients start with stage 4 clinical events, severe immunosuppression and very low CD4 counts. The ART-LINC collaboration (18 treatment programmes in Africa, Asia and South America) recorded a 4% mortality rate in 2725 patients under active follow-up six months after starting therapy but noted that mortality fell to 2% in the subsequent six months of therapy. The DART trial reported that 39 of 62 deaths (63%) in a cohort of over 1000 adults followed for two years occurred in the first six months of therapy.

In the Médecins Sans Frontières (MSF) cohort of over 6000 patients treated with a generic FDC of d4T + 3TC + NVP, almost 70% of deaths occurred during the three first months after ART initiation.[26] This greater risk of death is seen especially in patients with disseminated TB (and other severe OIs) and a pre-ART CD4 cell count <50 cells/mm³. [27][28][29]

6.4. Immune reconstitution inflammatory syndrome

The immune reconstitution inflammatory syndrome (IRIS) is a spectrum of clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery.[30] It can present with the signs and symptoms of a previously subclinical and unrecognized opportunistic infection, as a paradoxical worsening of treatment response several weeks into therapy, or as an autoimmune disease such as Graves disease (hyperthyroidism) in the context of immune recovery on ART. Typically, IRIS occurs within two to twelve weeks of the initiation of ART, although it may present later. The incidence of IRIS is estimated to be 10% among all patients initiating ART and up to 25% among patients initiating ART with a CD4 cell count below 50 cells/mm³.[31][32] However, the clinical syndromes associated with IRIS in resource-limited settings have been relatively poorly described and it is not known whether there are any important regional variations in the clinical spectrum.

Risk factors predicting the likelihood of IRIS include initiating ART close to the time of diagnosis of an opportunistic infection, being antiretroviral-naive at the time of diagnosis of an opportunistic infection, initiating ART when the CD4 count is below 50 cells/mm³, and having a more rapid initial decrease in the HIV-1 RNA level in response to ART than in patients with higher CD4 counts. [33]

IRIS has been reported in association with a large number of HIV-related infections and inflammatory conditions.[34][35] The most frequently occurring IRIS events are associated with

mycobacterial disease (tuberculosis or *Mycobacterium avium* complex infection) and cryptococcal disease. Together, mycobacterial and cryptococcal disease account for approximately 60% of all cases of IRIS in developed country settings.[36]

IRIS may be mild and resolve without treatment, e.g. it may involve a transient flare of hepatic enzymes in a patient with HIV/hepatitis B coinfection, or it may be severe and life-threatening, as in patients with cryptococcal meningitis or tuberculosis.[37] [38] The development of a new or recurrent OI soon after ART initiation does not indicate treatment failure and is not an indication to stop or switch ART. If possible, ART should be continued and the OI or inflammatory condition should be treated.[39] If this is impossible, ART should be temporarily interrupted, the OI or inflammatory condition should be treated, and the same ART regimen should be restarted.

The management of IRIS includes treatment of the causative pathogen in order to decrease the antigenic load, continuation of ART, and the use of corticosteroids. The dose and duration of corticosteroid treatment is unclear. Prednisolone (or prednisone) at 0.5 mg/kg/day for five to ten days is suggested in moderate to severe cases of IRIS.[40]

7. MANAGEMENT OF ANTIRETROVIRAL DRUG TOXICITIES

Antiretroviral agents are responsible for a broad range of toxicities, ranging from low-grade intolerances that may be self-limiting to life-threatening side-effects. One of the many challenges of the public health approach is to develop educational tools for patients and health care providers which can assist with the ready identification of drug-specific side-effects so that appropriate measures to alleviate or eliminate them can be taken. This is essential for patient safety and if drug adherence is to be maintained and interruption of treatment avoided.

Differentiating between complications of HIV disease and ART toxicity (also known as adverse events) is sometimes difficult. Alternative explanations for a patient's presenting symptoms should be considered before it is concluded that toxicity is ART-related. Considerations include intercurrent illness (e.g. hepatitis A virus infection in patients with symptoms of hepatitis, or malaria in patients with severe anaemia), or a reaction to medications other than ARVs, e.g. isoniazid-induced hepatitis or peripheral neuropathy, and rash induced by co-trimoxazole.

Drug-related adverse events can occur early (the first few weeks or months of treatment) and late (after six months or more of treatment). Adverse events can vary in severity from mild to severe and life-threatening. ARV toxicity may be specific to the drug or to the class of drugs in use.

Table 5. Common ARV toxicities

Haematological toxicity	Drug-induced bone marrow suppression, most commonly seen with AZT (anaemia, neutropenia).
Mitochondrial dysfunction	Primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy, lipoatrophy, myopathy.
Renal toxicity	Nephrolithiasis, commonly seen with IDV. Renal tubular dysfunction is associated with TDF.
Other metabolic abnormalities	More common with PIs. Include hyperlipidaemia, fat accumulation, insulin resistance, diabetes and osteopenia.
Allergic reactions	Skin rashes and hypersensitivity reactions, more common with the NNRTI drugs but also seen with certain NRTI drugs, such as ABC and some PIs.

Substitution within the first-line regimen in the context of individual drug toxicity is recommended. The decision to substitute a new ARV depends on the ability to attribute the toxicity to a specific ARV drug and on the severity of the toxicity symptoms (see Table 6).

As a general principle, mild toxicities do not require discontinuation of therapy or drug substitution, and symptomatic treatment may be given. Moderate or severe toxicities may require substitution with a drug in the same ARV class but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved. NNRTIs have a longer half-life than NRTIs, leading to a concern that stopping all drugs simultaneously may lead to exposure to drugs from the NNRTI class only and the possibility of resistance developing to the NNRTIs. However, if the patient has a life-threatening toxicity, all ARV drugs should be stopped simultaneously until the patient is stabilized. If the toxicity is attributable to the NNRTI component the concern about resistance may not matter, as NNRTIs may not be subsequently used.

Estimating severity grade (see Annex 7 for details)

GRADE 1 **Mild.** *Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.*

GRADE 2 **Moderate.** *Limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.*

GRADE 3 **Severe.** *Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.*

GRADE 4 **Severe life-threatening.** *Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care.*

Regardless of their severity, adverse events may affect adherence to therapy. A proactive approach to managing toxicity is recommended. Discussing the potential side-effects of the ART regimen with the patient before the initiation of therapy and during the early stages of treatment, as well as support during minor and moderate adverse events, can increase the likelihood of adherence to therapy (see Section 16). The patient should be familiar with signs and symptoms of toxicities that are serious and require immediate contact with the health care team. This is particularly important for toxicities that can be life-threatening, including NVP-associated Stevens-Johnson syndrome, hepatitis, lactic acidosis or ABC-associated hypersensitivity reaction.

Table 6. Guiding principles in the management of ARV drug toxicity

1. Determine the seriousness of the toxicity.

2. Evaluate concurrent medications and establish whether the toxicity is attributable to an ARV drug or drugs or to a non-ARV medication taken at the same time.

3. Consider other disease processes (e.g. viral hepatitis in an individual on ARV drugs who develops jaundice) because not all problems that arise during treatment are caused by ARV drugs.

4. Manage the adverse event according to severity. In general:

   • **Grade 4 (severe life-threatening reactions):** Immediately discontinue all ARV drugs, manage the medical event (i.e. symptomatic and supportive therapy) and reintroduce ARV drugs using a modified regimen (i.e. with an ARV substitution for the offending drug) when the patient is stabilized.[a]

   • **Grade 3 (severe reactions):** Substitute the offending drug without stopping ART.[a]

   • **Grade 2 (moderate reactions):** Consider continuation of ART as long as feasible. If the patient does not improve on symptomatic therapy, consider single-drug substitutions.[a]

   • **Grade1 (mild reactions)** are bothersome but do not require changes in therapy.

5. Stress the maintenance of adherence despite toxicity for mild and moderate reactions.

6. If there is a need to discontinue ART because of life-threatening toxicity, all ARV drugs should be stopped until the patient is stabilized.

a   See Table 7 for substitution options.

7.1.   Toxicity rates and types in ARV rollout programmes

Most initial regimens used in ARV scale-up since 2003 have included AZT or d4T with 3TC and NVP or EFV. The predominant toxicities have included the adverse events expected from the use of these drugs in other settings, e.g. anaemia, peripheral neuropathy, lactic acidosis, and, in cohorts with more than one year of treatment, lipoatrophy.

In a study in India between 1996 and 2004, 1443 ART-naive patients received regimens containing d4T or AZT. The most common toxicities were rash (66%), hepatotoxicity (27%) and anaemia (23%).[41] In Abidjan, Côte d'Ivoire, 498 adults with a median baseline haemoglobin of 113 g/l started AZT + 3TC + EFV; 118 patients had grade 3/4 neutropenia and 23 had grade 3/4 anaemia. Of these patients, 80% were taking co-trimoxazole, which can cause anaemia and neutropenia.[42] In the DART study being conducted in Uganda and Zimbabwe, 219 of 3314 participants (6.6%) developed grade 4 anaemia by week 48; in the same study, ABC hypersensitivity reactions were reported in 2% of participants.

In Tororo, Uganda, 1073 patients were treated with d4T + 3TC + NVP. The probabilities of remaining free of severe toxicity at 6, 12 and 18 months were 92%, 86% and 84% respectively, whereas nearly 50% of the patients experienced some form of toxicity by 18 months. Toxicity requiring a change in therapy occurred in 21% of the cohort, most commonly a switch from d4T to AZT. In Nairobi, Kenya, 284 patients received d4T + 3TC + NVP and the reported toxicity-free survival rate was 21% at 18 months. However, over 95% of patients remained on their original regimen despite these events. In a report from Khayelitsha, South Africa on 1700 patients receiving ART, one agent was substituted in approximately 10% because of toxicity. The rates were similar for d4T (8.5%), AZT (8.7%) and NVP (8.9%).

7.2. Metabolic complications and morphological changes

The major ART-related metabolic abnormalities are lactic acidosis, dyslipidaemia, morphological changes (fat accumulation and lipoatrophy), dysregulation of glucose metabolism, and reduced bone mineral density. The cluster of metabolic abnormalities together with fat redistribution (peripheral lipoatrophy and central fat accumulation) have been termed the *HIV lipodystrophy syndrome*. Adverse metabolic effects of potent antiretroviral therapy are a major concern because they may stigmatize the patient and because hyperlipidaemia and insulin resistance may increase the long-term risk of cardiovascular disease.[43] Rates of metabolic complications have been relatively poorly recorded in ART programmes in resource-limited settings. Better data are needed and improved pharmacovigilance is an important programme priority.

7.2.1. Lactic acidosis

Lactic acidosis is a rare but severe complication of NRTI therapy caused by mitochondrial dysfunction arising from the inhibition of mitochondrial DNA polymerase by NRTIs. Rates of lactic acidosis have been reported to be highest in regimens containing d4T. Symptomatic hyperlactataemia often develops slowly and is characterized by several non-specific symptoms including dyspnoea or hyperventilation, abdominal pain, fatigue and weight loss. Because the symptoms can be vague a high index of suspicion is needed. Routine monitoring of lactate levels in asymptomatic patients is not recommended. The measurement of serum lactate in a symptomatic patient is recommended if available.[2] Recently, point-of-care testing for lactate in rural settings has been reported.[44] A study in South Africa showed that women with a high body mass index (BMI) who had received d4T for more than six months were at particular risk of developing hyperlactataemia or lactic acidosis. The management of symptomatic hyperlactataemia includes the discontinuation of all ARVs. The need for hospital admission depends on the severity of the symptoms and on lactate levels if these are available. Recovery from lactic acidosis is often slow. When ART is restarted it should not include d4T or AZT. In cases of lactic acidosis a minimum of four weeks should be allowed before the reintroduction of an alternative regimen (e.g. substituting TDF or ABC for d4T or AZT).

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2   In settings where serum lactate is not available, calculating the anion gap (anion gap = [Na + K] – [HCO3 + Cl], normal 6−12 mmol/l), is an alternative.

7.2.2. Lipoatrophy

Lipoatrophy is characterized by the loss of subcutaneous fat in the face, arms, legs, abdomen and/or buttocks, with preservation of muscle mass. Risk factors for the development of lipoatrophy include older age and treatment with NRTIs. It is most commonly associated with d4T but occurs with all thymidine NRTIs. Some clinical trials and observational studies have demonstrated that d4T therapy is associated with an approximately twofold increased risk of lipoatrophy compared with AZT.[45][46][47] Other studies have consistently demonstrated that body fat tends to remain stable or even increase in the first 6 to 12 months of therapy and then to decline over the subsequent 12 to 24 months among patients receiving d4T or AZT-based treatment.[48][49] Because NRTI substitution strategies may be capable of at least halting the progression of lipoatrophy, it is important to monitor the rate and severity of fat loss in patients treated with d4T or AZT and to consider intervening before lipoatrophy becomes severe. The preferential management involves substitution of d4T or AZT with either TDF or ABC, which are predicted to cause less mitochondrial toxicity. There is evidence suggesting that the incidence of lipoatrophy can be reduced if initial regimens include either TDF or ABC in place of thymidine analogues.[50][51] If TDF and ABC are not available, some experts consider the option of reducing the dose of d4T to 30 mg twice daily in all patients irrespective of body weight, which may alleviate mitochondrial-associated complications without compromising antiviral activity.[17] However, it has to be recognized that d4T-related toxicities are cumulative and that the current therapeutic strategies for managing or reversing lipodystrophy are relatively ineffective.

7.2.3. Fat accumulation

Localized accumulation of adipose tissue in the upper trunk, anterior neck, dorsocervical fat pad, abdomen and breasts has been well described for patients receiving potent combination ART. These changes appear to occur independently of lipoatrophy. Fat accumulation has been observed in both PI-treated and non-PI-treated patients. Risk factors include older age, lower CD4 count at the initiation of therapy, higher body mass index before therapy and white race. Switching from a PI-based therapy to an NNRTI-based or NRTI-based regimen does not appear to improve fat accumulation.

Surgical options exist for both lipoatrophy (facial filling with collagen, synthetic polymers or silicone, or autologous fat transplantation) and lipodystrophy (liposuction). These options provide cosmetic improvement but may only give temporary benefit, especially if the patient continues to take an ARV drug that is associated with fat redistribution.

7.2.4. Dyslipidaemia

PIs (with the exception of unboosted atazanavir[52]), EFV and NRTIs can cause elevations in triglycerides and cholesterol. d4T and AZT are associated with greater rises in triglycerides and cholesterol than TDF in treatment-naive patients. Severe triglyceride elevations (i.e. grades 3 or 4, see Annex 7) may be associated with pancreatitis. Routine monitoring of lipid levels is not currently feasible in many settings and is not needed to support ART.

8. DRUG SUBSTITUTIONS BECAUSE OF TOXICITY

The general principle is that single-drug substitution because of toxicity should involve drugs belonging to the same ARV class. If toxicity is related to an identifiable drug in a regimen the offending drug can be replaced with one that does not have the same side-effects (e.g. substitution of AZT or TDF for d4T in cases of neuropathy, TDF or d4T for AZT where anaemia occurs, or NVP for EFV for CNS toxicity or in pregnancy). Given the limited number of ARV drug options available in resource-limited settings, drug substitutions should generally be limited to situations where toxicity is moderate to severe (grade 3) or life-threatening (grade 4) (see Annex 7).

Table 7 lists the usual ARV substitution options in instances of toxicity involving the ARVs recommended in first-line regimens.

Table 7. Toxicities of first-line ARVs and recommended drug substitutions

ARV drug	Common associated toxicity	Suggested substitute
ABC	Hypersensitivity reaction	AZT or TDF or d4T
AZT	Severe anaemia [a] or neutropenia [b] Severe gastrointestinal intolerance [c]	TDF or d4T or ABC
	Lactic acidosis	TDF or ABC [d]
d4T	Lactic acidosis Lipoatrophy / metabolic syndrome [e]	TDF or ABC [d]
	Peripheral neuropathy	AZT or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent and severe central nervous system toxicity [f]	NVP or TDF or ABC (or any PI [h])
	Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP or ABC (or any PI [h])
NVP	Hepatitis	EFV or TDF or ABC (or any PI [h])
	Hypersensitivity reaction	TDF or ABC (or any PI [h])
	Severe or life-threatening rash (Stevens-Johnson syndrome) [g]	

a   Exclude malaria in areas of stable malaria; severe anaemia (grade 4) is defined as Hb <6.5 g/dl.

b   Defined as neutrophil cell count <500/mm^3 (grade 4).

c   Defined as severe, refractory gastrointestinal intolerance that prevents ingestion of ARV drug regimen (e.g. persistent nausea and vomiting).

d   Reinitiation of ART should not include d4T or AZT in this situation. TDF or ABC is preferred.

e   Substitution of d4T may not reverse lipoatrophy.

f   e.g. persistent hallucinations or psychosis.

g   Severe rash is defined as extensive rash with desquamation, angioedema, or a reaction resembling serum sickness; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis; Stevens-Johnson syndrome can be life-threatening. For life-threatening rash, substitution with EFV is not recommended, although this approach has been reported in a small number of patients in Thailand without recurrence of rash.

h   PI class should be preferentially reserved for second-line therapy as no potent regimens have been identified for recommendation following initial PI failure (see Section 5.7).

The substitution of EFV for NVP following a non-severe (grade 1 or 2) NVP-related rash and/or hepatotoxicity is recommended, together with careful monitoring **[B-IV]**.

For life-threatening or more complex clinical situations, consultation with and/or referral to district or regional hospital centres is recommended. When a severe or life-threatening toxicity occurs it is appropriate to temporarily discontinue the entire ARV regimen until the toxicity has resolved. A revised regimen can then be introduced.

For some life-threatening toxicities it may not be possible to identify an optimal substitute drug within the drug class concerned. For example, in the case of NVP-associated Stevens-Johnson Syndrome, substitution with another NNRTI drug is not recommended because of the potential for class-specific toxicity **[B-IV]**, although this approach has been evaluated in a small number of patients in Thailand without recurrent rash. This situation would require a change to either a triple NRTI regimen (e.g. substituting a third NRTI, e.g. ABC or TDF, for NVP if AZT/3TC was the original dual NRTI component), or substituting a protease inhibitor for NVP, thereby introducing a drug class reserved for second-line regimens. If a PI is used, it must be noted that no potent and durable regimens have been identified for recommendations following initial PI failure (see Section 5.7).

9. ANTIRETROVIRAL TREATMENT FAILURE AND WHEN TO SWITCH THERAPY

The decision on when to switch from first-line to second-line therapy is critical. If the decision is made too early the months or years of potential further survival benefit from any remaining first-line effectiveness is lost; if it is made too late, the effectiveness of second-line therapy may be compromised and the patient is put at additional and appreciable risk of death. The time of switching is dictated by treatment failure, and this can be measured in three ways: clinically, by disease progression and WHO staging; immunologically, using trends in CD4 counts over time, and virologically, by measuring HIV viral loads (plasma HIV-1 RNA levels). However, the definitions of clinical, immunological and virological failure currently used in different settings represent different biological end-points. It is not clear which criteria are optimal, as either individual measures or a mix of measures. There is an urgent need for agreement on defining treatment failure and for standardization across the different ways of identifying it.

There is a limited amount of data and programme experience which can inform decisions about the optimal time to switch therapy in the first-line/second-line approach based on any of these monitoring strategies. Second-line regimens have not been widely available in the public sector, and even where they are available, first-line therapy has proved highly effective with little (clinical) failure identified at up to three years of follow-up. There are also significant constraints in using each of the three different approaches to the definition of failure.

- It is difficult in most facilities in resource-limited settings to make an accurate clinical (i.e. etiological) diagnosis of treatment failure because the possibilities for laboratory investigation are limited. If clinical correlates alone are used it is likely that many patients will switch with advanced disease, at appreciable risk of death from opportunistic infections, and will have high viral loads with extensive drug resistance.

- The value of immunological monitoring in defining ART failure largely depends on having a baseline CD4 count before commencing ART and on having longitudinal CD4 measurements on ART. One-off (spot) CD4 counts on ART are difficult to interpret when making decisions about treatment success or failure.

- Viral load measurements are not widely available and will remain restricted because of cost and accessibility. Switching therapy with any detectable virus (as recommended in industrialized countries where multiple individualized treatment regimens can be used) is an extremely conservative definition of failure and is too early in the public health approach. An appropriate threshold for switching regimens remains to be determined and is a research priority; some evidence suggests that 5000 to 10 000 copies/ml may be an appropriate threshold.[53] [54] [55] [56]

For the purposes of these guidelines, recommendations for switching from first-line to second-line therapy are based on the assumption that most countries only make provision for second-line regimens in the public sector. In this circumstance, premature switching to the second-line regimen needs to be avoided. The situation is further complicated because, for many programmes, monitoring is based primarily on clinical criteria, and even if CD4 cell count monitoring is available its frequency is probably limited. This clinical situation represents another argument for having CD4 cell quantitation universally available in resource-limited settings and for moving as quickly as

possible to develop affordable viral load monitoring (see Section 15). In all cases, adherence counselling is indicated and clinical judgement should be included in decision-making.

Table 8. Clinical, CD4 cell count and virological definitions of treatment failure for patients on a first-line antiretroviral regimen

Clinical failure [a]	New or recurrent WHO stage 4 condition [b c]
CD4 cell failure [d]	• Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • persistent CD4 levels below 100 cells/mm^3 [e]
Virological failure	Plasma viral load above10 000 copies/ml [f]

a   Current event must be differentiated from the immune reconstitution inflammatory syndrome.

b   Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections), may be an indication of treatment failure and thus require consideration of second-line therapy.

c   Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy.

d   Without concomitant infection to cause transient CD4 cell decrease.

e   Some experts consider that patients with persistent CD4 cell counts below 50/mm^3 after 12 months on ART may be more appropriate.

f   The optimal viral load value at which ART should be switched has not been defined. However, values of more than 10 000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline.

9.1. Clinical disease progression as an indicator of treatment failure

It should not be concluded, on the basis of clinical criteria, that an ARV regimen is failing until there has been a reasonable trial of first-line therapy lasting at least six to twelve months, adherence has been assessed and optimized, intercurrent opportunistic infections have been treated and resolved, and IRIS has been excluded. Clinical events that occur before the first six months of therapy are excluded from this definition of failure because they often represent immune reconstitution inflammatory syndromes related to pre-existing conditions (see Section 6).

The development of a new or recurrent WHO stage 3 or 4 condition on treatment (but after the first six months of ART) is considered functional evidence of HIV disease progression. This is being referred to as T staging, where T refers to the staging event on treatment. The assumption is that with immune restoration on ART, and the subsequent progressive immunodeficiency with a failing ART regimen, the clinical events signalling immune failure will be the same as those heralding advanced and then severe immunodeficiency without ART. Table 9 indicates how clinical staging on ART can be used as an indicator of failure and prompts consideration of the need to switch therapy.

Table 9. Clinical staging events to guide decision-making on switching

New or recurrent event on ART [a]	Recommendations	Additional management options
Asymptomatic (T1)	Do not switch regimen	• Maintain scheduled follow-up visits, including CD4 monitoring (if available) • Continue to offer adherence support
Stage 2 event (T2)	Do not switch regimen [b]	• Treat and manage staging event • Assess and offer adherence support • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Schedule earlier visit for clinical review and consider CD4 (if available) [c]
Stage 3 event (T3)	Consider switching regimen [b d]	• Treat and manage staging event and monitor response • Assess and offer adherence support • Check if on treatment for at least six months • Check CD4 cell count (if available) [c d] • Assess continuation or reintroduction of OI prophylaxis • Institute more frequent follow-up
Stage 4 event (T4)	Switch regimen [b e]	• Treat and manage staging event and monitor response • Check if on treatment for at least six months • Assess continuation or reintroduction of OI prophylaxis • Check CD4 cell count (if available) [c] • Assess and offer adherence support

a   Refers to clinical stages while on ART for at least six months (termed T1, T2, T3, T4).

b   Differentiation of opportunistic infections from immune reconstitution inflammatory syndrome is necessary.

c   Treat and manage the staging event before measuring CD4 cell count.

d   Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections) may be indicators of treatment failure and thus require consideration of second-line therapy; response to appropriate therapy should be used to evaluate the need for switching of therapy.

e   Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not be indicators of treatment failure and thus do not require consideration of second-line therapy; response to appropriate antimicrobial therapy should be used to evaluate the need to switch therapy.

TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ART (see Section 12). With pulmonary TB and some extrapulmonary TB diagnoses (e.g. simple lymph node TB or patients with uncomplicated pleural disease), where a good response to TB therapy is frequently seen, the decision to switch ART can be postponed and monitoring can be increased. This also applies if severe and/or recurrent bacterial infections (as stage 3 or 4 events) or oesophageal candidiasis respond well to therapy.

9.2.   CD4 count as a sign of immunological treatment failure

The CD4 cell count remains the strongest predictor of HIV-related complications, even after the initiation of therapy.[57] [58] The baseline pretreatment value is informative: lower CD4 counts are associated with smaller and slower improvements in counts. However, precise thresholds that define treatment failure in patients starting at various CD4 levels are not yet established. As a general rule, new and progressive severe immunodeficiency as demonstrated by declining longitudinal CD4 cell counts should trigger a switch in therapy. Ideally, any measurement that may indicate the need to consider switching should be repeated and the low level confirmed before any change is implemented.

Patients starting with low CD4 counts may demonstrate slow recovery, but persistent levels below 100 cells/mm^3 represent significant risk for HIV disease progression. Caveats to be noted are that intercurrent infections can result in transient CD4 count decreases, and that, with relatively infrequent monitoring (e.g. every six months), the true peak of the CD4 cell count may be missed. As a general principle, intercurrent infections should be managed, time should be allowed for recovery and the CD4 cell count should be measured before ART is switched. If resources permit, a second CD4 cell count should be obtained to confirm immunological failure.

Reasonable working definitions of immunological failure are: (1) CD4 count below 100 cells/mm^3 after six months of therapy; (2) a return to, or a fall below, the pre-therapy CD4 baseline after six months of therapy; or (3) a 50% decline from the on-treatment peak CD4 value (if known).

The CD4 cell count can also be used to determine when not to switch therapy, e.g. in a patient with a new clinical stage 3 event for whom switching is being considered or in a patient who is asymptomatic and under routine framework. In general, switching should not be recommended if the CD4 cell count is above 200 cells/mm^3.

9.3.   Plasma viral load as an indicator of treatment failure

Although viral load testing is not yet widely available, it is a sensitive and informative way to identify treatment failure. When treatment failure is defined on the basis of clinical and/or CD4 criteria the diagnosis may be made later than when viral load is being monitored. Diagnosing treatment failure based on clinical or CD4 criteria alone will provide a greater opportunity for the selection of drug resistance mutations before regimen change and may compromise particularly

the NRTI component of the second-line regimen through increasing class-wide drug resistance. This provides another strong argument for moving towards the wider availability of plasma viral load testing in resource-constrained settings. In particular, simple point-of-care assays are needed which identify, qualitatively or semiquantitatively, viral load thresholds that inform clinical management decisions.

Viral load testing is already available in some centres and programmes. However, the viral load threshold triggering a switch in ART is not defined. For the purposes of these guidelines, virological failure is defined as a plasma HIV-1 RNA level above 10 000 copies/ml in a person who has been on a regimen for more than six months and in whom drug adherence is determined to be sufficient. This level has been chosen on the basis of the association of viral load levels greater than 10 000 copies/ml with subsequent clinical progression[59] and appreciable CD4 cell count decline.[60]

Virological success is defined as a plasma HIV-1 RNA level below the limit of detection of the assay being used (e.g. values below 400 or below 50 copies/ml after six months of treatment). An undetectable viral load mandates that ART should not, in general, be switched irrespective of the CD4 cell count or the clinical stage.

Some programmes have established a local panel of experts to review cases under consideration for second-line therapy for this reason. Clinical status, the CD4 cell count, and the plasma HIV-1 RNA level (if available) can be used in an integrated fashion to determine whether HIV disease is progressing on therapy and whether a change from first-line to second-line therapy should be made. Table 10 provides guidance on deciding when to switch the treatment regimen if clinical status is considered in relation to the CD4 count alone or to the CD4 count plus viral load data. Clinical judgement remains an important part of the decision-making process.

Table 10 Integrating clinical status, CD4 cell count and viral load to guide switching

Treatment Failure Criteria	Who Stage 1	Who Stage 2	Who Stage 3	Who Stage 4
CD4 failure [a] (Viral load testing not available)	Do not switch regimen. Follow patient for development of clinical signs or symptoms. Repeat CD4 cell count in three months.	Do not switch regimen. Follow patient for evidence of further clinical progression. Repeat CD4 cell count in three months.	Consider switching [b] to second-line regimen.	Recommend switching [b] to second-line regimen.
CD4 failure [a] and viral load failure [c]	Consider switching [b] to second-line regimen.	Consider switching [b] to second-line regimen.	Recommend switching [b] to second-line regimen.	Recommend switching [b] to second-line regimen.

a   CD4 failure is defined as a fall to (or below) the pretreatment baseline or a 50% drop from the on-treatment peak level or persistent levels below 100 cells/mm^3.

b   Switching from first-line to second-line regimen for treatment failure should not be done until the first regimen has been given sufficient time to succeed. This should be a minimum of six months. Since only one second-line regimen is available in most circumstances, premature switching should be avoided.

c   Virological failure is provisionally defined as a plasma HIV-1 RNA level above 10 000 copies/ml after a minimum of six months on therapy.

10. CHOICE OF SECOND-LINE REGIMENS FOR TREATMENT FAILURE

WHO recommends that the entire regimen be changed if treatment failure occurs. The new second-line regimen has to involve drugs that retain activity against the patient's virus strain and should ideally include a minimum of three active drugs, one of them drawn from at least one new class, in order to increase the likelihood of treatment success and minimize the risk of cross-resistance **[A-III]**. The PI class is thus reserved for second-line treatments, preferably supported by two new NRTIs.

10.1. Choice of protease inhibitors in second-line therapy

The key element in the construction of an effective second-line regimen for treatment failure is the PI component, as this represents a potent drug from an entirely new (not previously used) class of agents. Maximizing the potency of the PI component is critical for successful virological suppression and durability of response. For this reason, a ritonavir-boosted PI (e.g. ATV/r, FPV/r, IDV/r, LPV/r or SQV/r) is recommended as the core of the second-line regimen **[A-II].**

There are insufficient data on the differences between ritonavir-boosted PIs to allow the recommendation of one agent over another. LPV/r has the advantage of being available as an FDC; moreover, the recent approval of a heat-stable tablet formulation eliminates the need for refrigeration. For other PIs to be boosted, ritonavir in heat-stable formulation is also desirable, particularly in countries with hot climates, but it has not been developed. When a heat-stable formulation becomes available or if the requirement for a cold chain is not a major issue for a country programme, then any of a number of RTV-boosted PIs can be chosen. WHO recommends that, if LPV/r is not an option, the alternative boosted PI be selected from SQV/r, ATV/r and FPV/r **[B-III]**. IDV/r is effective but the incidence of nephrolithiasis and the daily fluid requirement make this choice less attractive **[C-II]**. In the absence of a cold chain and in advance of the availability of the new formulation of LPV/r, NFV is an acceptable alternative choice for the PI component, although it is less potent than a boosted PI.[61] [62]

Fig. 2 indicates the second-line strategies to be considered in adolescents and adults who experience failure on the first-line regimens identified in Fig. 1

Standard second-line option if NRTI/NNRTI approach used in first-line therapy

ddI or TDF

PI/r [1]

EFV or NVP

NRTI-sparing option if triple NRTI approach used in first-line therapy

ABC or 3TC (± AZT) [2]
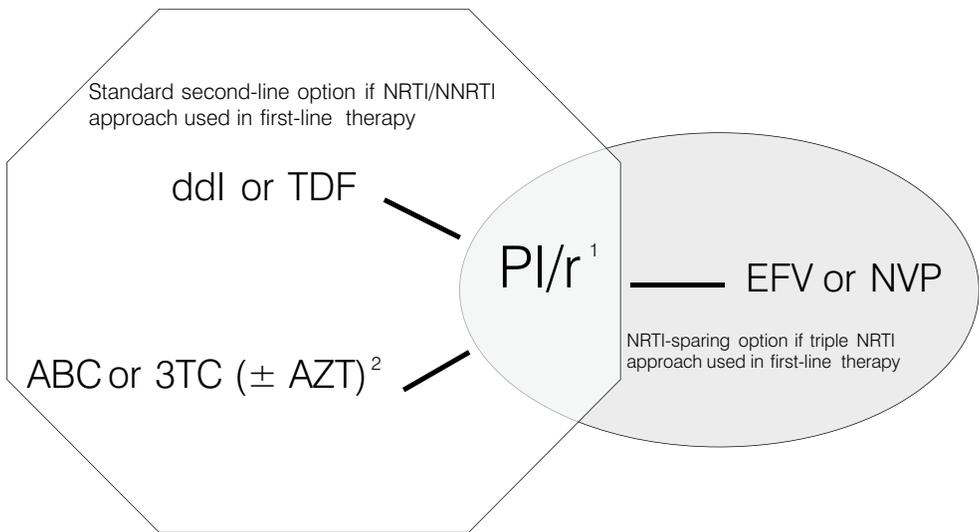
1   Ritonavir-boosted PIs (ATV/r, FPV/r, IDV/r, LPV/r and SQV/r) are considered as the key components in second-line regimens and their use should be reserved for this situation. LPV/r is the only PI currently available as an FDC and a new formulation that does not need refrigeration was recently launched. In the absence of a cold chain and where the new LPV/r formulation is not available, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

2   3TC (± AZT) is included for strategic use as resistance to both drugs is predicted to be present following failure on the respective first-line regimen listed. 3TC maintains the M184V mutation which may potentially decrease viral replicative capacity as well as induce some degree of resensitization to AZT or TDF; AZT may prevent or delay the emergence of the K65R mutation. It must be stressed that the clinical efficacy of this strategy in the situation envisaged has not been proved.

10.2. Choice of NRTIs in second-line therapy

The basic principle is ideally to support the chosen boosted PI with a dual NRTI backbone composed of two unused NRTIs. Among the previously unused NRTIs, ddI is a key drug for the construction of second-line regimens.[63] It is available in different concentrations as buffered or enteric-coated (EC) formulations. The buffered formulation is widely available and less costly. However, it is frequently associated with diarrhoea and other gastrointestinal side-effects. The EC formulation presents a better gastrointestinal tolerance, but is currently more expensive and less available in resource-limited settings than buffered formulations. There are also limited data on experience with the use of ddI EC formulations in these settings.

When failure has been identified clinically or immunologically, many patients can be expected to have significant NRTI resistance at the time of switching. With respect to nucleoside class cross-resistance and drug interactions, empirical alternative choices have to be made so as to provide maximal antiviral activity. Cross-resistance exists between d4T and AZT, and second-line regimens that offer more activity include ddI/ABC or TDF/ABC as dual NRTI components. The

issues of cost and drug hypersensitivity with ABC remain and high-level AZT/3TC resistance confers diminished susceptibility to ABC. TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but often retains activity against nucleoside-resistant viral strains. It should be noted that two of the recommended dual NRTI backbones in second-line regimens (ddI/ABC and TDF/ABC) may facilitate the evolution of the K65R drug resistance mutation, which mediates resistance to non-AZT NRTIs. Finally, the combination of TDF and ddI should be used with caution because of suboptimal CD4 cell responses and increased toxicity with this dual NRTI component.[64] [65] [66] If this combination is used the ddI dose should be adjusted for body weight in order to reduce the risks[67] [68] [69] (see Annex 3).

However some experts now recommend continuing 3TC in the setting of treatment failure because it may confer a viral replicative defect and/or residual antiviral activity.[70]

10.3. Boosted PI/NNRTI for patients in whom first-line triple NRTI therapy fails

Two new classes of ARVs are available for constructing the second-line regimen in patients who have had exposure only to NRTIs in the first-line regimen. The recommended combination is a boosted PI plus an NNRTI with the option to add ddI and/or 3TC to the boosted PI/NNRTI combination. Several studies have examined the NRTI-sparing approach of combining a boosted PI and NNRTI. One study[71] randomized 31 patients receiving standard therapy with two NRTIs plus lopinavir (and with VL below 80 copies/ml) in order to continue this regimen or replace the two NRTIs with NVP. At 48 weeks all patients maintained viral suppression. In a study in Thailand,[72] 60 patients in whom NRTI therapy failed were enrolled in a single-arm, open-label study of IDV/r 800 mg /100 mg twice a day plus EFV 600 mg once a day. The proportions of patients with undetectable VL (below 50 copies/ml) at weeks 49 and 96 were 87% and 69% respectively.

10.4. Other approaches

Several groups and studies[73] [74] are evaluating strategies for simplifying or enhancing long- term second-line therapy. The strategy of consolidating to boosted PI monotherapy following an initial phase of three-drug therapy is under evaluation in treatment-naive patients, and the initial results appear promising. The strategy has many similarities with standard TB treatment, with induction followed by a maintenance phase; unlike TB treatment, however, ART does not have an end-point representing cure. If the results continue to show promise, an induction/maintenance approach may prove an important simplification strategy for long-term delivery and adherence to second-line therapy, and this deserves further investigation. Additional studies are evaluating a dual boosted PI approach to second-line ART for patients in whom there is failure of two NRTIs/NNRTI. However, both approaches are at the stage of being investigated and neither strategy is recommended.

Table 11. Detailed recommendations for switching to second-line ARV regimens in adults and adolescents

First-line regimen		Second-line regimen	
		Rti component	Pi component [a]
Standard strategy	AZT or d4T + 3TC [b] + NVP or EFV	ddI + ABC or TDF + ABC or TDF + 3TC (± AZT) [c]	PI/r [d]
	TDF + 3TC [b] + NVP or EFV	ddI + ABC or ddI + 3TC (± AZT) [c]	
	ABC + 3TC [b] + NVP or EFV	ddI + 3TC (± AZT) [c] or TDF + 3TC (± AZT) [c]	
Alternative strategy	AZT or d4T + 3TC [b] + TDF or ABC	EFV or NVP ± ddI	

a   NFV does not need refrigeration and can be used as a PI alternative in places without a cold chain.

b   3TC and FTC are considered interchangeable because they are structurally related and share pharmacological properties and resistance profiles.

c   3TC can be considered to be maintained in second-line regimens to potentially reduce viral fitness, confer residual antiviral activity and maintain pressure on the M184V mutation to improve viral sensitivity to AZT or TDF. AZT may prevent or delay the emergence of the K65R mutation.

d   There are insufficient data to detect differences among currently available RTV-boosted PIs (ATV/r, FPV/r, IDV/r, LPV/r and SQV/r) and the choice should be based on individual programme priorities (see text). In the absence of a cold chain, NFV can be employed as the PI component but it is considered less potent than an RTV-boosted PI.

11. CONSIDERATIONS FOR WOMEN OF CHILDBEARING POTENTIAL OR PREGNANT WOMEN

The guiding principle for treatment of women of childbearing potential or pregnant women is that therapeutic decisions should be based solely on their need and eligibility for ART as outlined in Section 5 **[A-III]**. The special circumstances of pregnancy and breastfeeding raise additional issues of toxicity to mother and child, choice of ARV drug, and prevention of HIV transmission from mother to child (PMTCT), but these concerns should be dealt with in the context of assuring optimal treatment to preserve the mother's health. Consequently, the recommended WHO first-line regimen for this patient subgroup is an NVP-based scheme supported by two NRTIs. An EFV-based regimen is suitable for women with access to consistent and reliable contraception or for pregnant women after the first trimester of pregnancy who will have access to consistent and reliable contraception in the postpartum period.

11.1. Women of childbearing potential

The choice of ART for women with the potential to become pregnant requires consideration of the possibility that the ARV drugs may be received early in the first trimester, before recognition of pregnancy and during the primary period of foetal organ development. The ARV drug of most concern is EFV. Significant CNS defects have been observed in infant monkeys with *in utero* EFV exposure at drug levels similar to those seen with human exposure at standard therapeutic doses, and in four human infants with first trimester exposure to EFV-containing regimens.[75 76 77] EFV should therefore be avoided in women of childbearing potential who are not receiving adequate contraception, because of possible teratogenicity **[A-III]**. Women who are receiving ART and do not wish to become pregnant should have effective and appropriate contraceptive methods available in order to reduce the likelihood of unintended pregnancy. In women for whom effective contraception can be assured, EFV remains a viable option for the NNRTI component of the regimen.

11.1.1. Interaction of ART with hormonal contraceptives

Drugs that affect liver microsomal enzyme activity may increase the metabolism of ethinyl estradiol and norethindrone in oral contraceptives, resulting in lower serum levels of the hormones and lowered contraceptive efficacy. ARV drugs that can affect the CYP 450 liver enzyme system include the PIs and, to a lesser extent, the NNRTIs. There are only limited data on the interactions between oral contraceptives and ARVs. Lower ethinyl estradiol levels have been observed in women receiving concomitant NVP, RTV, NFV, LPV/r and SQV/r.[78 79] Ethinyl estradiol levels are slightly increased by ATV and IDV but are decreased by RTV; they are also slightly increased by the use of concomitant EFV but, because the pharmacokinetic interactions between EFV and oral contraceptives are not fully characterized and first-trimester exposure to EFV should be avoided, it is recommended that women receiving EFV use a reliable method of barrier contraception in addition to, or instead of, oral contraception **[A-III]**. The use of condoms is recommended for all women, regardless of hormonal contraceptive use, as condoms offer protection against other sexually transmitted diseases as well as HIV superinfection. Additional or alternative contraceptive approaches (consistent use of condoms) should be used in order to avoid pregnancy in women receiving PI and NNRTI drugs. It is not known if the contraceptive efficacy of preparations such as medroxyprogesterone acetate depot injection, which provide higher blood hormone levels than oral contraceptives, would be compromised. Preliminary data from one study that evaluated

pharmacokinetic interactions between medroxyprogesterone acetate and NVP-, EFV- or NFV-containing ART over a 12-week period indicated no significant differences in the antiretroviral drug levels between baseline and four-week evaluations, and no ovulation was observed during the 12-week study, suggesting that effective contraceptive efficacy may be maintained.

11.2. Pregnant women

11.2.1. Initiating ART in pregnant women

ART is recommended for pregnant women in accordance with the same eligibility criteria as for non-pregnant adults: it should be initiated in pregnant women with WHO clinical stage 3 or stage 4 disease, or in those with WHO clinical stage 1 or 2 disease and CD4 counts below 200 cells/mm^3 **[A-IV]**. It is also recommended that any pregnant woman with a CD4 count below 350 cells/mm^3 and WHO clinical stage 3 disease should initiate ART. The optimal time to initiate ART if the CD4 count is between 200 and 350 cells/mm^3 is unknown. There are additional benefits for PMTCT with this recommendation, and benefits for the mother in situations where single-dose NVP is used for PMTCT. There is a growing body of data indicating that viral suppression may be compromised if NNRTI-based ART is initiated less than six months following exposure to single-dose NVP (see Section 11.2.5), and it is likely that many women with CD4 counts between 200 and 350 cells/mm^3 require therapy to begin within the first year postpartum. Some experts suggest that ART be considered for pregnant women with stage 1 or 2 and CD4 cell counts below 350 cells/mm^3, particularly if the CD4 values are near the threshold of 200 cells/mm^3 **[C-IV]**.

While it may be desirable to initiate ART after the first trimester in order to minimize the potential for teratogenicity, the benefit of early therapy clearly outweighs any potential foetal risks and therapy should be initiated in such cases **[A-IV]**. Once started, ART should be continued postpartum.

11.2.2. Choice of first-line ARVs in pregnant women

There is only limited information about the safety of ART for pregnant women and their infants. The choice of ARV drugs in pregnant women is complex and requires several competing factors influencing risk and benefit to be weighed. These include:

- what treatment is recommended for the health of the woman in question;
- what is and is not known about the effects of the drugs on the pregnant woman and her infant (including toxicity and teratogenicity) and about potential long-term effects of *in utero* exposure on the child;
- efficacy for PMTCT (see WHO guidelines for PMTCT).

11.2.3. Choice of NRTI backbone

The ARV drugs with which the greatest clinical experience has been gained in pregnant women are AZT and 3TC, the preferred NRTIs for use in such women when available **[A-1]**. Alternative NRTI drugs for use in pregnancy include ABC, d4T and ddI. However, the dual NRTI combination of d4T/ddI should be avoided in pregnancy. It should be employed only if no other alternatives exist. This is particularly important because of the increased risk of lactic acidosis with this combination in

pregnant women. There are no data on the use of FTC in pregnancy, although data on other NRTI drugs suggest that standard dosing would be appropriate. There are scant data on the use of TDF during pregnancy. Studies in infant monkeys with *in utero* TDF exposure have not demonstrated gross congenital abnormalities but have shown decreased fetal growth and a reduction in fetal bone porosity within two months of the commencement of maternal therapy.[80] Additionally, bone demineralization has been observed in some infected children receiving chronic TDF-based therapy.[81] The clinical significance of these findings for children with *in utero* TDF exposure is unknown. Because of the lack of data on use in human pregnancy and concern regarding potential fetal bone effects, TDF should only be considered as a component of initial ART in pregnant women if other alternatives are not available or are contraindicated **[C-IV]**. However, for a woman receiving TDF who becomes pregnant the regimen may be continued; alternatively, AZT could be substituted for TDF during the pregnancy **[C-IV]**. Additionally, for women receiving TDF because of toxicity or resistance concerns related to other NRTI choices or as part of second-line therapy, the benefits of continuing therapy outweigh theoretical risks of infant toxicity.

11.2.4. Choice of NNRTI

NVP is the NNRTI of choice in pregnancy, because of extensive clinical experience with this drug in pregnant women and its proven efficacy in reducing MTCT **[A-I]**. However, symptomatic NVP-associated hepatic toxicity or serious rash, while uncommon, are more frequent in women than in men and more likely to be seen in antiretroviral-naive women with higher CD4 cell counts (above 250 cells/mm^3).[82] [83] [84] It is not known if pregnancy further predisposes women to such toxicities but cases have been reported in pregnant women.[85] [86] Since ART is recommended for pregnant women with WHO clinical stage 3 disease and CD4 counts below 350 cells/mm^3 there is heightened concern about the use of NVP in women with CD4 counts between 250 and 350 cells/mm^3 (see Section 11.2.5). For approaches to the treatment of pregnant women with CD4 counts between 250 and 350 cells/mm^3, see Table 12.

Pregnancy should be avoided in women receiving EFV-based therapy because of concerns about teratogenicity. EFV should be used during the first trimester of pregnancy only if the potential benefit justifies the potential risk to the fetus, e.g. in pregnant women without any other therapeutic options **[C-IV]**. If a woman is receiving EFV-containing ART and becomes pregnant, and if this is recognized during the first trimester, EFV should be discontinued and replaced by another drug. Because symptomatic NVP-associated hepatotoxicity has been primarily observed in antiretroviral-naive patients in whom NVP-based ART is being initiated, NVP could be substituted for EFV with close monitoring in women with higher CD4 counts. Alternatively, a PI-based or a triple NRTI regimen could be substituted. If a woman is already in the second or third trimester when pregnancy is recognized, EFV could be continued because the high-risk exposure has already occurred.[87] The exposure and risk should be discussed with the patient and adequate contraception should be ensured when the women is in the postpartum period.

11.2.5. NVP-based therapy in women with CD4 counts between 250 and 350 cells/mm^3: additional considerations

NVP is the NNRTI of choice for the initial treatment of women, as many infected women are of childbearing potential. EFV is not recommended for such women unless effective contraception is

being used, because of the potential for teratogenicity of EFV with first- trimester exposure. Severe symptomatic, and rarely fatal, hepatic toxicity associated with chronic NVP therapy is more frequent in females, most commonly occurring in the first six to twelve weeks of therapy. It is likely that hepatic toxicity is in part an immune-mediated phenomenon as it is more common in women with CD4 cell counts above 250 cells/mm^3 and in men with CD4 counts above 400 cells/mm^3.[88] [89] [90] [91] An analysis of several studies in the USA revealed that symptomatic hepatic toxicity occurred in 1−2% of women receiving NVP-based therapy who had CD4 counts below 250 cells/mm^3, with no cases of fatal hepatic toxicity,[89] [91] whereas among women with CD4 counts above 250 cells/mm^3, 10−11% had symptomatic hepatic toxicity and fatal hepatic toxicity affected 0.7% of them. In the USA the NVP drug label states that NVP should not be initiated in women with CD4 counts above 250 cells/mm^3 or in men with CD4 counts above 400 cells/mm^3 unless the benefit clearly outweighs the risk.

Studies in women in some, but not all, resource-constrained settings have suggested that the risk of NVP-associated hepatic toxicity is lower than that reported in developed settings, and have not noted an association between toxicity and CD4 counts. These studies have reported grade 3 or grade 4 elevations in hepatic enzymes in 4% to 6% of women with a range of CD4 cell counts.[92] [93] [94] [95] [96] [97] In South Africa, however, higher rates of symptomatic severe hepatic toxicity were found in women in a trial where CD4 counts were above 200 cells/mm^3 at entry (mean 398 cells/mm^3).[98] The numbers reported to date remain relatively low and further data are needed on toxicity in different populations.

This creates a problem in respect of the treatment of women with CD4 counts between 250 and 350 cells/mm^3, for whom therapy is recommended if they are in WHO clinical stage 3. The exact risk of fatal hepatitis with NVP in women in this CD4 count range is unclear, as the data have only been presented for toxicity in approximately 200 women with CD4 counts in the range 250 to 399 cells/mm^3 in developed settings. Fatal symptomatic hepatitis was observed in 0.4% of women with CD4 counts in this range; in contrast, mortality was highest, 1.1%, in women with CD4 counts exceeding 400 cells/mm^3. In the published case reports with data on CD4 counts, many but not all of the women with symptomatic or fatal hepatic toxicity had CD4 counts above 350 cells/mm^3. There is probably a gradient of toxicity risk in women with CD4 counts above 250/mm^3, with the greatest risk in women having a more normal immune status, as observed in women without HIV infection who received NVP-based post-exposure prophylaxis.[99] [100] Thus no data are available allowing determination of the extent of risk of symptomatic or fatal hepatitis in women with CD4 counts between 250 and 350 cells/mm^3.

The approaches to the treatment of women with CD4 counts between 250 and 350 cells/mm^3 including the following: treating with NVP and maintaining close observation over the first 12 weeks of therapy, as the benefit potentially could outweigh the risk; starting EFV and ensuring effective contraception (although in a recent study of 548 women receiving EFV in Côte d'Ivoire the yearly incidence of pregnancy was 2.6% despite counselling and the use of hormonal contraception);[101] starting a triple NRTI regimen; delaying therapy until the CD4 count has fallen below 250 cells/mm^3; starting a PI-based regimen **[C-IV]**. Each of these approaches has advantages and disadvantages (Table 11) and there are no data favouring one approach over any other. There is a pressing need for better information about NVP toxicity in women and for research in this area.

If NVP-based therapy is initiated in women with CD4 counts between 250 and 350 cells/mm^3, close monitoring is recommended during the first 12 weeks. This should include: education of the patient on symptoms of concern, for which she should return to the clinic (e.g. rash, fever, abdominal pain); more frequent visits in the first weeks of therapy (e.g. every two weeks); evaluation of baseline liver enzymes and their frequent monitoring in the first 12 weeks (e.g. baseline and at 2, 4, 8 and 12 weeks, followed by symptom-directed evaluation). If liver enzymes increase to grade 3 or higher (ALT and/or AST exceeding 5.1 times the upper limit of normal) without an alternative explanation, NVP should be permanently discontinued. NVP should be discontinued immediately if any symptoms suggesting hepatic toxicity develop, including rash. In this event it is vital not to wait until liver enzyme results are available.

Table 12. Approaches to initial therapy in women with CD4 counts in the range 250 to 350 cells/mm^3

APPROACH	ADVANTAGES	DISADVANTAGES
Initiation of NVP-based therapy with close observation over first 12 weeks	• Reserves PI for second-line regimen • Consistent with standard recommendations	• Potential elevated risk of severe hepatic toxicity (extent to which is undefined)
Initiation of EFV-based therapy with assurance of effective contraception	• Reserves PI for second-line regimen • Consistent with standard recommendations • Less risk of hepatic toxicity	• Potential risk of teratogenicity if pregnancy occurs
Initiation of triple NRTI therapy*	• Reserves PI for second-line regimen • Less risk of hepatic toxicity	• Studies suggest less potent than NNRTI-based regimens • Unknown safety of TDF in pregnancy
Delaying of therapy until CD4 count drops below 250 cells/mm^3	• If not on ARVs, no risk of hepatic toxicity	• Risk of disease progression, particularly if symptomatic
Initiation of PI-based therapy	• Less risk of hepatic toxicity	• No second-line treatment options exist

* AZT/3TC/ABC or AZT/3TC/TDF

11.2.6. Choice of PI for second-line ART in pregnancy

The protease inhibitors for which the most experience and safety data in pregnancy have been obtained are SQV/r and NFV. While standard dosing of NFV (1250 mg twice daily) has been shown to produce acceptable drug levels in pregnant women, a number of studies have suggested that NFV levels are highly variable during pregnancy. Some data suggest that drug levels of the capsule formulation of LPV/r may be lower in pregnant women during the third trimester than postpartum;[102] however, another study has shown adequate plasma levels in the majority of women with standard dosing.[103] A study is assessing whether higher doses may be needed during late pregnancy (i.e. four capsules twice daily rather than three capsules twice daily). There are no data on drug levels of the heat-stable LPV/r tablet drug formulation in pregnancy; until further data are available, standard dosing of this formulation can be given. Drug levels of IDV are lower during pregnancy than postpartum; limited data suggest that IDV with low-dose ritonavir boosting may result in adequate levels. There are no data on ATV/r or FPV/r in pregnant women; until more data are available these PIs should be used only if no alternative is available.

11.2.7. Impact of prior ART exposure for prevention of mother-to-child transmission

Many women may have received ARVs for PMTCT before requiring ART for their own health. For ARV drugs for which a single point mutation is associated with the development of drug resistance (such as NVP or 3TC) the potential impact of prior exposure to non-suppressive regimens for PMTCT on subsequent treatment of the mother may be a concern. This is particularly so for single-dose NVP, as mutations associated with NVP resistance have been detected in a plasma virus and in the breast milk of women who have received single-dose NVP for PMTCT, and such mutations may be associated with cross-resistance with other NNRTIs.[104] [105] NVP resistance can also develop among women who are receiving ARV drugs during pregnancy and intrapartum if they have detectable viral replication at the time of administration of single-dose NVP.[106] [107] Factors associated with the development of NVP resistance following single-dose exposure include: higher maternal viral loads and lower CD4+ cell counts; viral subtype (rates are higher with subtypes D and C than with subtype A); number of maternal doses; and body compartment (rates may be higher in breast milk than plasma).[105] [108] [109] The frequency of detection of resistance mutations using standard assays is greatest near the time of drug administration and decreases over time, although mutations may persist at very low levels in some women for a prolonged period.[110] [111] Some data suggest that the incidence of resistance may be decreased if other ARV drugs are given intrapartum and for a short period postnatally following single-dose NVP.[112] [113] However, the optimal ARV regimen and duration of administration are not yet known. Data indicate that NVP levels may be detectable for as long as 21 days after the receipt of single-dose NVP.[114]

Resistance to 3TC is also associated with a single mutation. In a study in which 3TC was added to AZT therapy at 32 weeks of gestation in pregnant women in France, the 3TC resistance mutation M184V was observed at six weeks postpartum in 39% of them;[115] 3TC resistance was also detected at one week postpartum in 12% of women receiving AZT/3TC for four weeks in order to prevent MTCT in the PETRA study.[116] However, no AZT or 3TC resistance was observed with intrapartum administration of AZT/3TC at one week postpartum.[117]

The clinical consequences of selection of these resistance mutations in terms of response to future ART are unknown. A study in Thailand suggested that maximal viral suppression might be decreased in women who had received single-dose NVP and subsequently initiated NVP-based ART, although clinical and immunological responses did not differ from those where there was no single-dose NVP exposure.[118] The timing of initiation of NNRTI-based ART following single-dose NVP exposure may be important: a lower rate of maximal viral suppression may occur if ART is started less than six months after single-dose NVP exposure, whereas the response to therapy appears to be the same as in women without single-dose NVP exposure if ART is started six to eighteen months after exposure.[119] Studies are in progress and planned with a view to determining whether single-dose NVP prophylaxis compromises subsequent ART with NNRTI-based regimens. This major operational research question must be answered with appropriately conducted studies.

Until definitive data are available on these matters, women who have previously received single-dose NVP prophylaxis for the prevention of MTCT should be considered eligible for NNRTI-based regimens and should not be denied access to life-sustaining therapy. On the basis of current data, a triple NRTI regimen, when available, can be considered as an alternative to NNRTI-based therapy for initial treatment if ART is required to be started in women within six months of single-dose NVP exposure **[B-IV]**. An initial PI-based regimen can also be considered as an option in this situation, with the caveat that it then compromises the second-line treatment options **[C-IV]**. The use of an NNRTI-based regimen is recommended for women with single-dose NVP exposure who are initiating therapy more than six months after exposure **[A-III]**.

The risk of drug resistance is strongly associated with the maternal plasma viral load and the CD4 count at the time of exposure; consequently, the women most at risk of developing NVP resistance with exposure to single-dose NVP are those with more advanced HIV disease for whom the initiation of standard triple-drug combination therapy is recommended. One of the best ways to prevent the development of NVP resistance is to assess the need of all pregnant women for antiretroviral therapy, optimally including CD4 count evaluation, and to initiate standard suppressive therapy for those who require it.

11.2.8. Women who are breastfeeding

In most resource-limited settings, breastfeeding continues to be the most feasible, safe, accessible, affordable and sustainable option supporting adequate nutrition for HIV-exposed infants. However, breastfeeding is also an important route of postnatal HIV transmission, and there is a great need to develop interventions that reduce or eliminate this risk and secure adequate and safe nutrition for the infants. ART is recommended for postpartum breastfeeding women who meet the WHO criteria for the initiation of therapy for their own health. This symptomatic group of infected women, who have high viral loads and suppressed immune systems, is probably also the group with the highest risk of transmitting HIV to their infants through breastfeeding.

12. CONSIDERATIONS FOR PATIENTS WITH TUBERCULOSIS

Tuberculosis is an important entry point into HIV care and a common opportunistic infection among persons already diagnosed with HIV, particularly in resource-limited settings. HIV-infected persons with TB often require ART, and WHO recommends that ART be given to all patients with extrapulmonary TB (stage 4) and all those with pulmonary TB (stage 3) unless the CD4 count is above 350 cells/mm^3. ART reduces both case-fatality rates and the incidence of TB and recurrent TB.[120] [121]

Antiretroviral therapy in individuals undergoing treatment for TB merits special consideration because comanagement of HIV and TB is complicated by: drug interactions between rifampicin and both the NNRTI and PI classes; the immune reconstitution inflammatory syndrome (IRIS); pill burden; overlapping toxicities; and adherence issues.[122] Active TB can be present when ART needs to be initiated or can present in patients receiving first-line or second-line therapy. The treatment of active TB remains a priority for patient care. Collaboration between TB and HIV programmes is essential for the delivery of an integrated package of HIV and TB services.[123]

12.1. When to start first-line ART in patients with active tuberculosis

For patients with active TB in whom HIV infection is diagnosed and ART is required the first priority is to initiate standard antituberculosis treatment (in accordance with national TB policy and guidelines). The optimal time to initiate ART is not known. Case-fatality rates in patients with TB during the first two months of TB treatment are high, particularly in settings where there are high prevalences of HIV,[124] suggesting that ART should begin early. On the other hand, considerations of pill burden, drug-drug interactions, toxicity and IRIS support the later initiation of ART.

While awaiting the results of current research studies, WHO recommends that, in persons with CD4 cell counts below 200 cells/mm^3, ART should be started between two and eight weeks after the start of TB therapy when the patient has stabilized on TB treatment **[A-III]**. This provisional recommendation is meant to encourage rapid initiation of therapy in patients among whom there may be a high mortality rate. For patients with CD4 cell counts above 200 cells/mm^3 the commencement of ART may be delayed until after the initial intensive phase of TB treatment has been completed, in order to simplify the management of TB treatment and to deal with the challenges mentioned above **[A-III]**. In patients with CD4 counts above 350 cells/mm^3, ART can be delayed until after the completion of short-course TB therapy, following a reassessment of the patients eligibility for ART and evaluation of the response to TB therapy and of CD4 cell counts, if available.

In circumstances where CD4 cell counts cannot be obtained, WHO recommends that ART be initiated two to eight weeks after the start of TB therapy when the patient has stabilized on TB treatment. For some patients with uncomplicated pulmonary TB disease in whom a good response to TB therapy is seen, ART may be delayed until the initial intensive phase of TB treatment is completed. ART may also be deferred in selected cases of extrapulmonary TB (lymph node TB or patients with uncomplicated pleural disease) where a good response to TB therapy is seen (Table 13) **[A-IV]**.

Table 13. Initiating first-line ART in relationship to starting anti-TB therapy

CD4 cell count	ART recommendations	Timing of ART in relation to start of TB treatment
CD4 <200 cells/mm³	Recommend ART [a]	Between two and eight weeks [b]
CD4 between 200 and 350 cells/mm³	Recommend ART	After eight weeks
CD4 >350 cells/mm³	Defer ART [c]	Re-evaluate patient at eight weeks and at the end of TB treatment
Not available	Recommend ART [d]	Between two and eight weeks

a   An EFV-containing regimen is the preferred first-line regimen. Alternative first-line treatment regimens include NVP and triple NRTI (based on TDF or ABC) regimens. For NVP-containing regimens, ALT should be checked at 4, 8 and 12 weeks; treatment should be decided on the basis of symptoms thereafter.

b   ART should start as soon as TB treatment is tolerated, particularly in patients with severe immunosuppression.

c   ART should be started if other non-TB stage 3 or 4 events are present.

d   For some TB diagnoses that generally respond well to anti-TB therapy (i.e. lymph node TB, uncomplicated pleural effusion), deferral of ART should be considered.

12.2. What to start: recommended ART for patients with active TB

The recommended standard first-line ART regimen comprises two NRTIs plus one NNRTI. There are few drug interactions with TB drugs and the NRTI backbone and no specific changes are recommended. The situation is more complex with the NNRTI class because NNRTI levels are reduced in the presence of rifampicin. However, accumulating data support the use of first-line NNRTI-containing antiretroviral regimens in patients receiving rifampicin-containing treatment for TB. Here EFV is the preferred option, because the interactions with rifampicin are easier to manage; but the use of EFV may be limited by its restrictions in pregnant women or women of childbearing potential. NVP is an alternative agent, but carries the risk of hepatotoxicity, particularly in persons with higher CD4 counts or for whom no CD4 count is available.[125] The use of a triple NRTI regimen is emerging as an additional option[126] for first-line ART in TB patients with HIV-2 infection. An initial PI-based regimen can also be considered in HIV-2 infection, with the caveat that it will compromise second-line treatment options.

Two NRTIs + efavirenz

EFV blood levels are decreased in the presence of rifampicin. This can be overcome by a dose increase of 600 mg to 800 mg daily. Emerging evidence does not show any benefit in increasing the EFV dose to 800 mg/daily in patients weighing under 60 kg and receiving both EFV and rifampicin.[127 128 129 130 131] While awaiting more data on EFV dosing for persons weighing 60 kg and above, WHO recommends the standard 600-mg dose of EFV **[A-II]**. Because of concerns related to teratogenicity, EFV should not be used in women of childbearing potential without adequate contraception or in women who are in the first trimester of pregnancy **[A-III]**.

Two NRTIs + nevirapine

NVP levels are also decreased in the presence of rifampicin. However, given the high therapeutic index of NVP and the recent studies in South Africa and Thailand showing good short-term outcomes in antiviral activity and few adverse events in patients receiving both drugs, standard NVP dosing is recommended **[B-II]**.[132] [133] [134] [135] [136] This area requires further investigation as there is large interpatient variability in NVP levels among HIV-infected persons, independently of any rifampicin interaction. Because of concerns about safety, close clinical and laboratory monitoring of liver enzymes at weeks 4, 8 and 12 is advised for all patients receiving NVP plus rifampicin.

There are concerns about the risk of symptomatic or fatal hepatitis in women with CD4 counts between 250 and 350 cells/mm^3. The additional influence on the liver toxicity of rifampicin-containing regimens in this population is not known. Until further data are available, nevirapine-containing regimens should only be considered in life-threatening situations and when no alternative is available for women on rifampicin-containing regimens who have CD4 cell counts in the range 250 to 350 cells/mm^3 and need to start ART.

Triple NRTI regimens

Triple NRTIs are considered an alternative regimen in patients undergoing TB treatment. Two triple NRTI regimens (AZT + 3TC + ABC and AZT + 3TC + TDF) can be used safely with rifampicin. Furthermore, either regimen can be used in patients with higher CD4 cell counts where the risk of toxicity for nevirapine may be increased, and in special conditions (HBV-induced hepatitis and HIV-2 infection). Pregnant women can safely take AZT, 3TC and ABC, and this regimen has no drug interactions with rifampicin. Concerns for this triple NRTI regimen relate to antiviral potency, limited data for patients with TB, and hypersensitivity reactions. AZT, 3TC and TDF have no or minimal interactions with rifampicin but efficacy data are limited for patients with TB and hypersensitivity reactions.

12.3. Women of childbearing potential or pregnant women with TB who require ART

An EFV-containing regimen is the first-line treatment recommendation for patients with TB and HIV but should not be used during the first trimester of pregnancy or in women of childbearing potential unless effective contraception is ensured. If a pregnant woman is in the second or third trimester, an EFV-containing ART regimen can be considered. Effective contraception would have to be assured postpartum if the regimen were continued. An alternative in women with active TB is a triple NRTI regimen, e.g. AZT + 3TC + ABC. A change from an EFV-containing to an NVP-containing regimen can be considered when TB treatment has been completed.

12.4. Immune reconstitution inflammatory syndrome in patients diagnosed with TB who start ART

The immune reconstitution inflammatory syndrome (IRIS) may present as a worsening of clinical disease after initial improvement. It may occur in up to a third of persons with tuberculosis who initiate ART. IRIS typically presents within three months of the initiation of ART but can occur as early as five days. TB-associated IRIS most commonly presents with fever and a worsening of pre-existing lymphadenopathy or respiratory disease. It is similar to, but more frequent than, the paradoxical reactions seen in immunocompetent patients on antituberculosis therapy. Several reports suggest that IRIS is more common if ART is started early in the course of TB treatment and in patients with low CD4 counts. Most cases resolve without any intervention and ART can be safely continued. Serious reactions such as tracheal compression, caused by massive adenopathy, or respiratory difficulty, may occur. Therapy may require the use of corticosteroids (see Section 5).[137] [138] [139]

12.5. Tuberculosis in patients already receiving ART

There are two issues to consider in patients who are diagnosed with TB while on ART. The first concerns the modifications of ART, if any, which should be recommended for patients developing active TB within six months of initiating first-line or second-line ART. These recommendations are summarized in Table 14.

Table 14. ART recommendations for patients who develop TB within six months of starting a first-line or second-line ART regimen

First-line or second- line ART	ART regimen at the time TB occurs	Options
First-line ART	Two NRTIs + EFV	Continue with two NRTIs + EFV
	Two NRTIs + NVP	• Substitute to EFV [a] [b] or • Substitute to triple NRTI regimen [a] or • Continue with two NRTIs + NVP [c]
	Triple NRTI regimen	Continue triple NRTI regimen
Second-line ART	Two NRTI s + PI	Substitute to or continue (if already being taken) LPV/r- or SQV/r-containing regimen and adjust dose of RTV [a]

a   Substituting back to the original regimens once the rifampicin-containing regimen is completed can be considered. When switching back from EFV to NVP, no lead-in dose is required.

b   The use of EFV-containing regimens is not recommended in women of childbearing potential, if adequate contraception cannot be ensured, and during the first trimester of pregnancy.

c   Careful clinical and laboratory monitoring (ALT) is advised when NVP or boosted PIs are administered concurrently with rifampicin.

The second issue is whether the presentation of active TB on ART constitutes ART failure. In cohort studies, ART decreases the incidence of TB in treated patients by approximately 80%. Rates of TB among treated patients nevertheless remain persistently higher than among HIV-negative individuals.[122 140] An episode of TB can occur across a wide range of CD4 cell counts[141] and does not necessarily herald ART failure and the need to switch to second-line regimens. In addition, subclinical or undiagnosed TB often presents within the first six months after the initiation of ART, frequently as part of IRIS (see Section 6.1).[142]

WHO therefore recommends that the following principles be applied when determining whether the development of TB on ART constitutes treatment failure. If an episode of TB occurs during the first six months following the initiation of ART, this should not be considered a treatment failure event (see Section 9) and the ART regimen should be adjusted for coadministration with rifampicin-containing regimens **[A-IV]** (see Table 14).

If an episode of TB develops more than six months after the initiation of ART and data on the CD4 cell count and viral load are available, the decision about whether the TB diagnosis represents ART failure is based on the CD4 cell count and, if available, the viral load (see Section 9, Table 10). If a CD4 cell count is not available the decision on whether the TB diagnosis constitutes ART failure depends on whether the TB is pulmonary or extrapulmonary and whether there are other non-TB stage 3 or 4 events. While awaiting more data, WHO recommends that the development of an episode of pulmonary TB after six months of ART, without other clinical and immunological evidence of disease progression, should not be regarded as representing ART failure. Extrapulmonary TB should be considered as indicating ART failure, although simple lymph node TB or uncomplicated pleural disease may be less significant than disseminated TB. If there is a good response to TB therapy the decision to switch to a second-line regimen can be delayed until short-course TB therapy has been completed.

12.6. Constructing a second-line treatment regimen for patients with an episode of TB which indicates first-line ART failure

The effectiveness of second-line therapy for patients in whom an NNRTI regimen has failed depends on the introduction of PIs in the new regimen. However, there are significant drug interactions with the PIs and rifampicin. Consequently, the treatment options are constrained for patients who develop TB while on PIs or for whom TB heralds the failure of a first-line regimen (see above) and who require PI-based therapy.

Unboosted PIs cannot be used with rifampicin-containing regimens because protease inhibitor levels are subtherapeutic **[A-II]**.[143 144] Thus, if a patient needs to switch to or is already on a PI-based regimen, lopinavir 400 mg / ritonavir 400 mg twice daily in combination with rifampicin could be considered under close clinical and laboratory monitoring to detect hepatic toxicity **[B-IV]**. Full endorsement of this regimen requires further data. Alternatively, SQV 400 mg / RTV 400 mg can be considered, with the same close clinical and laboratory monitoring, but endorsement of this PI-based regimen also requires further data **[B-IV]**. Concerns about the

combinations of SQV 1000 mg / r 100 mg b.d. with rifampicin include high rates of hepatic toxicity reported in a study of HIV-uninfected volunteers and the potency of the combination. The use of this and other boosted PI combinations is discouraged until further data are available.[145] [146] [147] [148]

The recommendations and precautions for the use of PI-based regimens in combination with rifampicin in women of childbearing potential and pregnant women are the same as for other TB patients **[B-IV]**.

When rifabutin is used in place of rifampicin, other boosted PIs regimens can be administered. Dose adjustments are required in most situations and rifabutin is contraindicated in patients with WBCs below 1000/mm^3 and platelet counts below 50 000/mm^3. Moreover, this drug can cause uveitis. However, rifabutin may not be available or accessible in the public sector, and it is costly. Efforts should be made to reduce its cost and increase its availability at country level.

13. CONSIDERATIONS IN HEPATITIS B OR HEPATITIS C COINFECTION

Hepatitis B infection is endemic in many resource-limited countries. Shared modes of transmission lead to high rates of coinfection with HIV and hepatitis B virus (HBV) and/or hepatitis C virus (HCV) in many parts of the world.[149] It is estimated that between 370 million and 400 million people are chronic carriers of HBV and that 180 million are chronically infected with HCV. The prevalence of coinfection varies widely between geographical regions and between modes of HIV transmission.[150] Rates of HIV/HCV coinfection are highest in areas where injecting drug use and unsafe blood practices are the dominant modes of HIV transmission.

HIV modifies the natural history of HBV infection: higher rates of progression to advanced liver disease occur among persons with HIV/HBV coinfection.[151] The presence of HIV infection is associated with greater rates of progression to cirrhosis. The impact of HBV on the natural history of HIV is less certain.[152]

In the setting of HIV infection the course of HCV-associated liver disease is accelerated. Rates of progression of liver disease in HIV/HCV coinfection are greater.[153] As with HBV, there is contradictory evidence on the effects of HCV on HIV disease progression.[154] [155] [156] [157] In the Swiss cohort study the presence of HCV was independently associated with an increased risk of progression to AIDS and death. However, the EuroSIDA cohort analysis found that the overall virological and immunological responses to ART were not affected by HCV serostatus. There were no differences in the times needed to decrease viral loads to less than 400 copies or in the times needed to increase CD4 cell counts by 50% between HCV-positive and HCV-negative HIV-infected patients starting ART.[158] However, the risk of mortality related to liver disease was markedly increased in HCV-seropositive patients.[159]

13.1. HBV infection

13.1.1. Treatment of HBV

WHO advocates more widely available HBsAg testing, especially in areas of high hepatitis B prevalence. Guidelines have recently been developed for screening and the management of HBV and HIV therapy.[160] There are several antiviral agents with activity against HBV. Three of these drugs (3TC, FTC and TDF) also have activity against HIV and are recommended as first-line agents; they should be used in patients with HIV/HBV coinfection. 3TC and FTC share the same anti-HBV and anti-HIV activity and are interchangeable. They should not be used together.

Lamivudine (3TC) is efficacious against HBV in patients with and without HIV. The efficacy of 3TC is limited by the occurrence of HBV drug resistance, which develops in 50% of patients after two years of 3TC monotherapy for HBV and in 90% after four years of treatment.[161] HBV seroconversion (loss of HBeAg and development of HBe antibody) occurs in 11% to 22% of HBeAg-positive HIV-1-infected patients who are treated with lamivudine for one year. The discontinuation of 3TC without the inclusion of other anti-HBV drugs may be associated with hepatitis flares and rapid clinical deterioration.

Emtricitabine (FTC) appears to have similar rates of suppression of HBV DNA, a similar safety profile and a similar resistance pattern to those of 3TC.

Tenofovir (TDF) is effective against wild-type and 3TC-resistant HBV. On the basis of small studies in HIV patients the efficacy of TDF against HBV appears superior to that of 3TC.[162][163] There is growing interest in the use of combination therapy for HBV with TDF and either 3TC or FTC. The virological superiority of combination therapy with TDF and 3TC over monotherapy with 3TC in both 3TC-naive and 3TC-experienced HIV-coinfected patients has recently been demonstrated in preliminary studies.[164][165] However, the impact of combination therapy on the development of HBV resistance is currently under evaluation.

13.1.2. Selection of ART in patients with HIV/HBV coinfection

In situations where both HIV and HBV require treatment, the ART regimens must contain 3TC and/or TDF. It is preferable to use 3TC and TDF together as both drugs have anti-HIV and anti-HBV activity and the use of TDF or 3TC as the only anti-HBV drug can result in more rapid development of resistance.

For treatment-naive HIV-1-infected persons who require ART, either 3TC at 150 mg twice daily or 300 mg daily or FTC at 200 mg daily is recommended for the treatment of chronic HBV infection as part of the ART regimen. Because of the high rate of development of HBV resistance to 3TC monotherapy, and because preliminary data have demonstrated a superior virological response to combination therapy, the inclusion of TDF, where available, should be considered as part of the ARV regimen. ARV programmes in areas of the world with a high HBV seroprevalence and no capacity to screen for HBV may consider the use of TDF plus either FTC or 3TC as the preferred initial NRTI combination. EFV is the preferred NNRTI option, or a triple NNRTI combination may be used.

It is recommended that NVP be used with care and regular monitoring in patients who have known HIV/HBV coinfection and grade 3 or lower elevation of ALT. NVP is not recommended for those with ALT elevations of grade 4 or higher.

13.1.3. HBV flares on ART

HBV flares may occur during ART in HBV/HIV coinfection as a presentation of the immune reconstitution inflammatory syndrome (see Section 6.1). Flares are characterized by acute rises in hepatic transaminases accompanied by symptoms of acute hepatitis (fatigue, abdominal pain and jaundice). These reactions generally occur during the first few months of treatment and may be difficult to distinguish from ART-induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare, and, if the patient is receiving 3TC monotherapy, consideration should be given to the addition of TDF if available. If it is not possible to distinguish a serious hepatitis B flare from a grade 4 ART toxicity, all ARV drugs should be withheld until the clinical condition improves.

13.1.4. HBV flares when ART is stopped

There is also a risk of a flare of HBV when HBV-active drugs are stopped. Fatal cases of acute HBV have been documented in HIV/HBV coinfected patients who discontinue 3TC monotherapy. Patients with coinfection who need to stop the HBV-active drugs in the HIV treatment regimen (3TC, FTC or TDF) should be closely monitored. If a patient is known to have chronic HBV it is recommended that 3TC be continued as part of second-line ART following initial ART failure, even if it has been used in first-line treatment.

13.2 HCV infection

13.2.1. Treatment of HCV

Irrespective of whether a patient has HIV infection, the optimal treatment for hepatitis C virus infection is pegylated interferon alpha and ribavirin (RBV).[166] [167] These drugs are complex to deliver, costly and not generally available through the public sector in resource-limited settings. Guidelines on the use of these drugs have recently been published.[168]

> *The initiation of ART in HIV/HCV-coinfected patients should follow the same principles and recommendations as for the initiation of ART in HIV-monoinfected patients. However, the patients should be followed up more closely because of the major risk of drug-related hepatotoxicity and for specific drug interactions of some ARVs with anti-HCV drugs.*
> *The major interactions are:*
> * *Ribavirin and ddI –> pancreatitis/lactic acidosis (do not give concomitantly).*
> * *Ribavirin and AZT –> anaemia (monitor closely).*
> * *Interferon and EFV –> severe depression (monitor closely).*

In patients with high CD4 cell counts it is preferable to treat HCV infection before HIV. While concurrent treatment of both infections is feasible, it may be complicated by pill burden (RBV + ARV drugs), drug toxicities and drug interactions. In patients who need ART it may be preferable to initiate ART and delay HCV therapy in order to obtain better anti-HCV response rates after immune recovery.

13.2.2. Selection of ART in HCV coinfection

In general, recommendations for the selection of ART are not different for patients with HCV coinfection. Patients with HCV coinfection may experience increased rates of hepatotoxicity during ART compared to patients without HCV. Several studies have examined the impact of specific ART regimens on toxicity in HCV/HIV coinfection. A recent analysis from the EuroSIDA cohort found no differences between currently available nucleoside pairs or non-nucleoside/PI treatments in a large group of HCV-infected patients.[169]

EFV is the NNRTI of choice in patients with HIV/HCV coinfection. A triple NRTI regimen is also an option. It is recommended that NVP be used with care; if it is used in patients with HIV/HCV coinfection who have grade 3 or lower elevation of ALT, regular monitoring is recommended. NVP is not recommended in patients with ALT elevations of grade 4 or above.

13.2.3. ART in patients with baseline elevation of ALT and unknown HBV/HCV status

In resource-limited settings, baseline ALT may be available but HBV/HCV status may be unknown. Ideally, serological testing for viral hepatitis should be pursued when elevations of ALT are noted. As stated above, NVP-based ART should be used with caution in patients (whether their HBV/HCV status is known or not) who have baseline grade 1, 2 or 3 elevations of ALT, and regular monitoring should take place. NVP should not be used in patients with ALT elevations of grade 4 or above.

The introduction of an EFV-containing regimen is recommended after the withdrawal of NVP (for grade 4 ALT elevation and/or clinical hepatitis) and the stabilization of clinical status and ALT. If EFV is withdrawn (for grade 4 ALT elevation and/or clinical hepatitis), NVP should not be initiated; a triple NRTI regimen can be used.

Principles for initiating ART in IDUs
- *ART treatment should not be excluded or unnecessarily delayed in current or former IDUs.*
- *Issues related to comorbidities, treatment priorities and readiness to start ART should be adequately addressed from the scientific, social and ethical perspectives.*
- *A comprehensive approach to care and treatment of IDUs is recommended but the absence of specific components (e.g. opioid substitution therapy) should not be a barrier to starting ART in those who need it.*

The epidemiological importance of injecting drug use as a route of transmission of HIV varies considerably between and even within countries. Worldwide, it is estimated that there are more than 13 million injecting drug users (IDUs), the majority (about 80%) living in developing and transitional countries.[170] There are data indicating that IDUs may have lower and suboptimal access to HIV care and may be less likely to receive antiretroviral therapy than other populations.[171] [172] [173] In some settings, often in those countries where the HIV epidemic is largely driven by IDUs, this arises because of a lack of provision of ART in general and to IDUs in particular.[174] In settings where ART is available, disordered lives, criminalization and social marginalization are the major factors that adversely affect the provision of HIV care.[173] [174] Patients often present complicated pictures to carers, involving psychiatric illness, coinfection with TB, HBV and HCV, high incidences of bacterial infection, and polysubstance abuse. In addition, health care programmes often fail to recognize that drug dependence is a medical condition and frequently have a perception that drug users do not adhere to ART, overlooking the confounding effects of social instability, poverty, psychiatric morbidity, human rights violations and poor patient-physician relationships which characterize many drug users' lives. The need to improve adherence among IDUs is recognized but there is evidence suggesting that when engaged in stable care with experienced staff and adequate support, IDUs can adhere to ART and have clinical outcomes comparable to those of HIV patients who do not use drugs.[173] [175] Active drug use is therefore not a valid reason for denying IDUs access to treatmen and care.

Thus, from the biomedical, epidemiological and ethical points of view, drug use should not be used as an argument for withholding antiretroviral therapy from persons for whom treatment would otherwise be recommended. A comprehensive approach to care and treatment of drug dependence is recommended, but the absence of specific components (e.g. opioid substitution treatment − OST) should not be a barrier to starting antiretroviral therapy in patients for whom it is indicated.

The criteria for initiating ART and the first-line and second-line therapies in substance-dependent patients are the same as for the general population (see Sections 4 and 5).

The management of ART in IDUs may pose some challenges because of comorbidities, drug side-effects and toxicities, the need for substance dependence treatment, drug interactions, psychosocial problems and legal issues. Issues related to TB and viral hepatitis coinfection have been dealt with in sections 12 and 13 respectively.

Support is needed such that IDUs can fully access available treatment services and adhere strictly to treatment regimens. Adherence support should be part of the routine clinical care provided by health professionals and peer support groups involved in dealing with HIV-positive individuals.

The development of programmes that integrate care of drug dependence (including OST) and HIV is therefore encouraged where approaches such as directly observed therapy (DOT) can be considered. Harm reduction strategies are highly effective for IDUs in supporting HIV prevention, treatment and care. Appropriate support, provided by an accessible and nonjudgemental health care team and delivered through community-based programmes and outreach strategies, has proved effective. Comprehensive harm reduction programmes also reduce new HIV infections among IDUs.[176][77]

Whenever possible, preference should be given to antiretroviral regimens that include the drugs least likely to cause hepatic, renal, haematological or neuropsychiatric side-effects. Simple dosing schedules and the absence of interactions with, for example, methadone or buprenorphine, are also desirable characteristics. The use of specific strategies (fixed-dose combinations, once-daily drugs, directly supervised treatment, psychosocial support, case management) should be strongly considered in order to improve adherence to treatment.

It is important to note that methadone and buprenorphine are now on the WHO Essential Drugs List, a reflection of the world body's commitment to the health rights of IDUs (http://www.who.int/medicines/publications/essentialmedicines/en/index.html).

Patients receiving methadone replacement therapy and NNRTI-based ART require a stepwise increase in the daily dose of methadone of 5−10 mg to maintain pre-NNRTI methadone levels.

The dosage adjustment of methadone is normally required approximately seven days after commencing methadone and NNRTI coadministration **[A-II]***.*

Methadone is the most commonly used replacement drug for the treatment of opiate dependence. Since methadone interferes with gastric emptying and with metabolism by major cytochrome P450 isoenzymes, interactions with ART are common and may lead to symptoms of opiate withdrawal or overdose and/or to increased toxicity or to decreased efficacy of antiretroviral drugs. From the perspective of ART provision, important drug interactions exist between some ARVs and methadone, particularly the NNRTIs and certain PIs which can lower the levels of methadone and precipitate withdrawal symptoms. The latter normally occur after several days of coadministration and can be treated with stepwise increases in the daily doses of methadone. The use of EFV or NVP is associated with significant decreases in methadone levels, which can lead to opiate withdrawal symptoms. On the other hand, methadone does not affect NNRTI levels. With regard to the PIs, the use of amprenavir, NFV or LPV can result in decreases in methadone levels. NFV does not seem to be associated with opiate withdrawal but LPV/r has been associated with opiate withdrawal symptoms. SQV and ATV do not seem to affect methadone levels. Except for amprenavir, whose levels can be reduced by up to 30%, the available data indicate that the use of methadone does not significantly affect PI levels. Although the pharmacokinetics of methadone seem to be unaffected by NRTIs, methadone increases the area under the curve of AZT by 40%, which in turn may lead to a higher incidence of AZT-related side-effects. Methadone leads to a significant decline in levels of the buffered tablet formulation of ddI, but not of the enteric-coated formulation. Interactions with other NRTIs are not likely to be clinically relevant.

Buprenorphine is increasingly used for the treatment of opiate dependence. There are limited data on interactions with antiretroviral drugs. However, it appears that AZT in conjunction with buprenorphine does not increase AZT levels as is the case with methadone. Interactions with EFV, LPV/r and NFV can occur but do not seem to be clinically significant[178][179] **[A-III]**.

Annex 5 lists the major interactions between ARVs and methadone and buprenorphine.

Although HIV infection is most commonly associated with people who inject opiates, effective treatment options for dependence on other substances, e.g. cocaine and amphetamine-type stimulants (ATSs), should also be provided. At present there is no proven substitution therapy for stimulant injectors. Interventions that have been shown to be beneficial in the treatment of cocaine and ATS use and dependence include psychological interventions, cognitive behavioural therapy (CBT), the community reinforcement approach, contingency management and twelve-step programmes.

Challenges faced in the provision of ART to cocaine and ATS injectors are similar to those facing services dealing with opioid injectors. Special efforts to reinforce ART adherence should also be considered in this population.

15. CLINICAL AND LABORATORY MONITORING

In resource-limited settings, WHO recommends that clinical assessment be the primary tool for monitoring patients, both before the initiation of ART and after it has started. However, it is highly desirable to develop a laboratory monitoring protocol on a countrywide basis in order to improve the efficacy of therapeutic interventions and to ensure the maximum level of safety when ARV drugs are being delivered.

Clinical and laboratory monitoring of HIV-infected patients serves two purposes. Firstly, for patients under care who are not yet eligible for ART, regular monitoring is essential for the identification of the point at which they become eligible for ART or for prophylaxis against opportunistic infections (e.g. with co-trimoxazole). Well-designed monitoring protocols can facilitate the initiation of OI prophylaxis and ART in the majority of HIV-infected patients before they develop advanced HIV infection.

Secondly, once patients have been initiated on ART, regular monitoring is necessary to assess efficacy, manage side-effects and identify treatment failure. Regular monitoring is also essential for reinforcing ARV adherence, the most critical parameter in the success of ART programmes.

Because resources are limited, laboratory testing should generally be directed by signs and symptoms and should be done only when the results can be used to guide management decisions. Exceptions are the recommendations to obtain a CD4 cell count every six months **[A-IV]** and routine monitoring of haemoglobin in patients receiving AZT. Haemoglobin measurement is recommended before the initiation of AZT and at 4, 8 and 12 weeks on AZT treatment **[A-IV]**.

The critical decisions in HIV care and treatment are:

- when to start therapy (see Section 4);
- when to substitute one therapy for another because of significant side-effects (see Section 7);
- when to switch therapy because of treatment failure (see Section 9);
- when to stop therapy and move to end-of-life and palliative care (see Section 17).

15.1. Baseline clinical and laboratory assessment

Every patient diagnosed as having HIV infection should undergo a baseline clinical and laboratory assessment in order to determine the stage of HIV infection and eligibility for co-trimoxazole, ART and other interventions. The baseline assessment should be used to evaluate patients for the presence of active OIs, especially TB, and to serve as an entry point into chronic care. This assessment should also serve as a means to provide counselling and support in relation to secondary HIV prevention and the disclosure of HIV diagnosis to others.

Table 15. Recommended baseline clinical and laboratory assessments

Clinical assessment at baseline	• Clinical staging of HIV disease • Determination of concomitant medical conditions (e.g. HBV, HCV, TB, pregnancy, injecting drug use, major psychiatric illness) • Concomitant medications (including traditional and herbal medicines) • Weight • Assessment of patient readiness for therapy
Laboratory assessment at baseline	• Confirmation of HIV infection status • Measurement of CD4 where possible • Haemoglobin measurement if initiation of AZT is being considered • Pregnancy test in women if initiation of EFV is being considered • Screening for TB and malaria (and diagnostic testing for other coinfections and opportunistic diseases where clinically indicated)

15.2. Monitoring of patients who are not yet eligible for ART

Patients who are not yet eligible for ART should be monitored for clinical progression and by CD4 count measurement every six months. Clinical evaluation should include the same parameters as are used in baseline evaluations, including weight gain or loss and development of clinical signs and symptoms of progressive HIV disease. These clinical parameters and the CD4 cell count should be used to update the WHO disease stage at each visit and to determine whether patients have become eligible for co-trimoxazole prophylaxis or ART. Clinical evaluation and CD4 counts can be obtained more frequently as the clinical or immunological threshold for initiating ART approaches (Table 4).

15.3. Patients on ART: recommendations for clinical monitoring

The frequency of clinical monitoring depends on the response to ART. At the minimum, however, such monitoring should take place 2, 4, 8, 12 and 24 weeks after ART begins and should subsequently be performed every six months once the patient has stabilized on therapy **[A-IV]**. At each visit, contact with a member of the health care team trained to triage is recommended, with referral to a physician as needed. Many programmes dispense ART on a monthly basis, thus increasing the number of opportunities to monitor clinical progression or drug toxicity.

Once ART is in progress, clinical assessment at each visit is the same as for pre-ART (except for confirmation of HIV status), with the addition of counselling to assist the patient's understanding of ART and adherence support. Observation of the patient's response to therapy should also include assessment of symptoms of potential drug toxicities or treatment failure (i.e. reassessment of clinical stage). Particularly important signs of a patient's response to ART include a decreased frequency of infections (bacterial infections, oral thrush, and/or other opportunistic infections).

15.4. Patients on ART: recommendations for laboratory monitoring

Routine monitoring of CD4 cell counts (if available) is recommended every six months, or more frequently if clinically indicated. The TLC is not suitable for monitoring therapy as a change in the TLC value does not reliably predict treatment success.

For patients who are to be initiated on AZT-containing regimens, haemoglobin should be measured before initiation and at weeks 4, 8 and 12 on therapy or in response to symptoms **[A-IV]**. The measurement of ALT and other blood chemistries should be done in response to signs and symptoms; it is not recommended routinely **[B-IV]**. However, if NVP is initiated in women with CD4 counts between 250 and 350 cells/mm³, the monitoring of hepatic enzymes at weeks 2, 4, 8 and 12 after initiation is recommended if available, followed by monitoring based on clinical symptoms **[C-IV]**. The evaluation of renal function in patients can be considered before the initiation of TDF and every six months on TDF therapy **[C-III]**.

Hyperlactataemia and lactic acidosis can develop in some patients on NRTIs. It is recommended that the capacity to measure serum lactate be available at district or central laboratory level, especially for patients receiving d4T or ddl. Routine measurements of serum lactate are not useful in predicting the development of lactic acidosis. Serum lactate should only be measured when patients have signs or symptoms suggesting lactic acidosis[3] **[B-IV]**.

Protease inhibitors can adversely affect glucose and lipid metabolism. Some experts support routine monitoring of chemistry panels in patients receiving PI-based regimens. While such monitoring may be advisable for specific patients receiving protease inhibitors, the laboratory monitoring of lipids and glucose should generally take place in response to clinical symptoms and signs.

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3   In settings where serum lactate is not available, calculating the anion gap (anion gap = [Na + K] – [HCO3 + Cl], normal 6–12 mmol/l) is an alternative.

HIV viral load measurement is currently not recommended for monitoring patients on ART in resource-limited settings **[B-IV]**. The use of viral load testing should be considered primarily for the diagnosis of HIV infection in HIV-exposed infants aged under 18 months **[B-I]**. In adults and adolescents, viral load testing may contribute to the diagnosis of ART failure earlier than would happen if only clinical and CD4 monitoring were in place and in more complex cases, such as those with discordant clinical and immunological responses (see Section 9, Table 10) **[B-IV]**

Table 16. Recommended minimum frequency of laboratory tests for monitoring in resource-limited settings

Diagnosis and monitoring laboratory tests	Pre-art* (At entry into care)	At initiation of first-line or second-line arv regimen	Every six months	As required (Depending on symptoms)
HIV diagnostic testing	✓		-	-
Haemoglobin [a]		✓	-	✓
WBC and differential [b]	-	✓	-	✓
CD4 cell count [c]	✓	✓	✓	
Pregnancy testing [d]		✓	-	✓
Full chemistry (including, but not restricted to, ALT,[e] other liver enzymes, renal function, glucose, lipids, amylase, lipase, lactate and serum electrolytes) [f]	-	-	-	✓
Viral load measurement [g]	-	-	-	✓

a   Haemoglobin monitoring for patients on AZT is recommended at baseline and at weeks 4, 8 and 12 after initiation of AZT.

b   Monitoring at week 4, 8 and 12 after initiation of ART is optional.

c   Patients who are not yet eligible for ART should be monitored with measurement of CD4 every six months. For patients who develop WHO stage 2 events, or whose CD4 measurements approach threshold values, the frequency of CD4 measurement can be increased. Patients on ART should have CD4 measurement every six months if stable. More frequent CD4 monitoring may be necessary for deciding when to start or switch ART.

d   Pregnancy testing for women initiating a first-line regimen containing EFV, and if pregnancy is suspected in women who are receiving an EFV-based regimen.

e   The predictive value of routine liver enzyme monitoring is considered very low by some experts. WHO recommends liver enzyme monitoring in response to symptoms. However, regular monitoring during the first three months of treatment and symptom-directed measurement of liver enzymes thereafter has been considered by some experts for certain patients using nevirapine-based regimens, in particular for women with CD4 cell counts above 250 cells/mm^3 and for those coinfected with hepatitis B or hepatitis C virus or with other hepatic disease.

f   Regular monitoring (every six months), if available, of full chemistry tests, particularly lipid levels, ALT and renal function, should be considered for patients receiving second-line drugs.

g   Viral load measurement is not recommended for decision-making on the initiation or regular monitoring of ART in resource-limited settings. It is recommended primarily for the definitive diagnosis of HIV infection in HIV-exposed children aged under 18 months and may be considered in connection with diagnosing treatment failure earlier or to assess discordant clinical and CD4 findings in patients in whom it is suspected that ART has failed.

*   Pre-ART assessment is also used to decide if co-trimoxazole prophylaxis is indicated.

Adapted from the *WHO Consultation on Technical and Operational Recommendations for Scale-up of Laboratory Services and Monitoring HIV Antiretroviral Therapy in Resource-limited Settings*. Geneva: World Health Organization; 2005.

16. ADHERENCE TO ANTIRETROVIRAL THERAPY

Adherence to ART is well recognized as an essential component of individual and programmatic treatment success. Studies on drug adherence in the developed world have demonstrated that higher levels of drug adherence are associated with improved virological, immunological and clinical outcomes and that adherence rates exceeding 95% are necessary in order to maximize the benefits of ART.[180] [181] It is desirable to achieve rates of this order over a long period. Numerous approaches to improving adherence have been investigated in the developed world and have begun to be explored in resource-limited settings.[182] [183]

Particularly in the absence of HIV-RNA (viral load) for detecting early ART failure, adherence is even more crucial for delaying or avoiding the development of drug resistance and ensuring maximum durability of the first-line ARV regimen.

The contribution of dose timing is less well studied. A recent study demonstrated that a mean dose-timing error (DTE) of less than three hours over a one-month period was independently associated with virological suppression.[184]

A review of the efficacy of 24 adherence intervention studies published between 1996 and 2004 revealed that interventions targeting people with poor ART adherence had better outcomes. The most frequently reported interventions in this review were reminder systems and counselling support.[185]

The success of any adherence strategy depends on the education of patients before the initiation of ART, an assessment of their understanding of the therapy, and their readiness for treatment. Adherence counselling includes giving basic information on HIV and its manifestations, the benefits and side-effects of ARV medications, how the medications should be taken and the importance of not missing any doses. Peer counsellors and visual materials can be particularly useful in this process.

Once treatment has begun the keys to success include trying to minimize the number of pills (in part through the use of FDCs), the packaging of pills (coblister packs when available), the frequency of dosing (no more than twice-daily regimens), the avoidance of food restrictions, fitting the ARVs into the patient's lifestyle, and the involvement of relatives, friends and/or community members in supporting the patient's adherence.

After therapy has begun it is essential to continue with support for adherence. This should involve adherence assessments during every health centre visit, the emphasizing of adherence principles to the patient by treatment supporters, and the continuous involvement of relatives, friends and/or community support personnel. Although the coverage of ART in the developing world remains low in relation to the burden of disease, important lessons have been learnt which can be incorporated into newly developing or expanding programmes, as outlined below.

- Medications should be provided free of charge for people who can least afford treatment, through subsidized or other financing strategies. Free access to ARVs at the point of delivery may assist adherence.[186] Recent data from Botswana, Senegal and other African countries indicate that cost-sharing is detrimental to long-term adherence.[187] [188] These issues need further exploration.

- Family or community members should be engaged in adherence education and maintenance programmes. Home visits can be useful if the patient's status is known by family members. It is essential to minimize stigma through psychosocial support.

- Family-based care is desirable if more than one family member is HIV-infected. This is particularly true when mother and child are infected.

- Pillboxes or coblister packs can be used.

- Directly observed therapy (DOT) or modified DOT strategies can be adopted. This approach is resource-intensive and difficult to introduce on a large scale and for the lifelong duration of ART. However, it may be helpful for certain groups (IDUs) and for early patient training.

- Strategies are required for reaching isolated communities.

At the programmatic level it is vital to ensure adequate stocks and storage of ARVs and to provide necessary resources for culturally appropriate adherence counselling.

Adherence in women in the postpartum period may be particularly problematic and require special support for them, as the stresses of caring for a newborn baby may lead a woman to pay insufficient attention to her own health care.

Adherence in children is a special challenge, particularly if the family unit is disrupted by health, economic or political conditions. Family-based HIV care programmes are some of the best approaches to assuring childhood health. It is imperative that paediatric formulations be improved and made widely available. They should match the adult regimens, where possible, so that family-based care can be pursued effectively.

17. HEAVILY TREATMENT-EXPERIENCED PATIENTS AND WHEN TO STOP ART

These guidelines detail a public health approach to ART and consider only first-line and second-line antiretroviral regimens using the three different oral ARV classes of drugs. However, as programmes mature and greater penetration of antiretrovirals into populations becomes a reality there will be increasing numbers of patients who start to fail second-line therapies. Third-line, fourth-line and fifth-line therapies are a reality in industrialized countries, where there are possibilities for individualized patient management, routine viral load and drug resistance testing, and access to the full formulary of licensed ARVs.

For patients who start to experience treatment failure on a second-line regimen with no further treatment options, the failing ART regimen should be continued unless toxicities or drug interactions are making the clinical situation worse for the patient **[B-IV]**. Even with treatment failure the regimen is likely to have residual antiviral activity, and drug resistance mutations may confer a replicative defect in the virus, possibly restricting its fitness and pathogenicity to some extent. The M184V mutation associated with 3TC/FTC and the PI-associated mutations are most frequently linked to such effects. The discontinuance of therapy in the setting of virological failure can be associated with precipitous falls in CD4 cell counts and the occurrence of opportunistic complications.

If a patient has exhausted all available antiretroviral and OI treatment options and is clearly in a terminal condition because of advanced HIV infection or has distressing or intolerable side-effects of therapy, it becomes reasonable to stop giving ARVs and to institute an active palliative and end-of-life care plan.

Salvage options after a clinical failure of second-line ART are difficult to construct at the population level if all three available oral ARV classes have been fully used. For highly treatment-experienced patients, individual management is necessarily tailored to the availability of alternative ARVs, for which there is very limited provision in the public sector in resource-limited settings, and to additional laboratory investigations, such as individual drug resistance testing. If and when new ARVs emerge, salvage may be feasible. Work on drug development must take into consideration the needs of patients failing ART in resource-limited settings.

The expansion of ART programmes will inevitably be accompanied by the emergence of HIV drug resistance (HIVDR), which has occurred in all countries where antiretroviral therapy is routinely practised. The rapid or uncontrolled emergence of HIVDR is feared as a potential consequence of ART scale-up in resource-limited countries.[189]

Several factors may limit efforts to prevent the emergence of drug resistance in such countries. Given that switching from a first-line regimen to a second-line regimen is likely to be based on clinical failure, some patients will have experienced drug pressure with high rates of viral replication for periods ranging from days to months, and may have high levels of resistance to some drugs and drug classes in the first-line regimen. As second-line regimens become available it is important that information be available on a population basis to guide the selection of the best NRTIs to support the PI class in second-line regimens for particular countries. Other factors may also increase the risk of resistance emerging, including limited numbers of trained health workers and facilities, and difficulties in drug supply continuity that may accompany rapid expansion. However, other aspects of treatment programmes in resource-limited countries may limit the risk. ART can be delivered successfully through the national implementation of rational ART guidelines on the basis of the "three ones" principles[190] (one agreed HIV/AIDS action framework for coordination, one national AIDS coordinating authority, and one agreed country-level monitoring and evaluation system). The use of optimal simplified highly active first-line combination regimens in resource-limited countries can support a high degree of viral suppression on a population basis. The sequential use of regimens inadequate to suppress viral replication is unlikely where publicly available first-line and second-line regimens are standardized and frequently available as fixed-dose combinations. The availability of a limited number of potent standardized regimens can limit aberrant prescribing practices and unnecessary regimen switching. Finally, where public ART programmes are standardized and coordinated at national level in resource-limited countries, large-scale changes to optimize programme practices can be made relatively quickly. Efforts to ensure that evidence-based programme monitoring occurs countrywide are based on a system developed by a large number of organizations and countries for monitoring key treatment-related variables,[191] many of which are directly relevant to evaluating HIVDR prevention.

In addition to the general measures listed, WHO recommends that a specific strategy to evaluate and limit HIVDR be included in all national HIV prevention and treatment plans. The objectives of the WHO HIVDR strategy for countries are: (1) to use a standard methodology for regular population-level evaluations of HIVDR emergence and transmission; (2) to implement ongoing evaluation of ART programme factors potentially associated with HIVDR emergence; and (3) to support evidence-based recommendations for maintaining the effectiveness of ART regimens and limiting HIVDR transmission.

With a view to the development and implementation of the strategy, WHO HIVResNet, a global network of over 50 HIVDR clinical, laboratory, epidemiological and research experts and organizations, has been set up. Members support WHO and the genotyping laboratory network in the development of protocols and guidelines, criteria and assessment tools, and the global database. Members also assist WHO in providing technical assistance in countries for HIVDR strategy implementation.

Preventing unnecessary emergence and transmission of HIV drug resistance at the population level

WHO's public health principles for minimizing HIVDR involve:

- appropriate ART access, prescribing and usage;

- fostering adherence;

- supporting the prevention of HIV transmission;

- appropriate action based on HIVDR surveillance and monitoring results.

The programme elements whereby these principles are implemented include:

- the formation of a national HIV drug resistance working group in each country, convened by the ministry of health or the national AIDS committee, to plan and implement a coordinated HIVDR prevention and evaluation strategy;

- the use of standard highly active ART regimens;

- quality assurance for ARVs;

- adequate and continuous drug supplies;

- standardized individual treatment records;

- support for and monitoring of adherence;

- removal of barriers to continuous access to care;

- linking prevention programmes to ART programmes so as to reduce secondary transmission of HIV infection;

- surveillance of HIV drug resistance in order to assess transmitted drug resistance in newly infected individuals in specific geographical areas of each country;

- surveys of HIVDR at sentinel ART sites and related ART programme factors;

- institutionalized monitoring of key early warning indicators which may be programmatically improved to minimize the emergence of HIVDR.

Surveillance of transmitted HIVDR

Models have demonstrated that substantial transmission of HIVDR is unlikely in the early years of ART scale-up in resource-limited countries.[192] WHO recommends a minimum resource method for surveillance of HIVDR transmission to indicate when drug resistance transmission is sufficiently substantial to be detected, at which time additional prevention and evaluation measures may be considered. The methodology utilizes remnant specimens, preferably from individuals covered by HIV seroprevalence surveys who are likely to have been recently infected, i.e. individuals under 25 years of age and, in the case of pregnant women, in their first pregnancy. If available, evidence in the form of a valid laboratory test indicating recent infection is an additional criterion.

A maximum of 47 remnant specimens from consecutive eligible HIV-positive specimens from each specific geographical area are sequenced in the *pol* gene to identify HIVDR mutations, and prevalence is categorized for each drug and drug class as under 5%, 5% to 15%, or over 15% for each area. If HIV serosurvey specimens are not available, HIV diagnostic specimens from newly diagnosed individuals likely to have been recently infected are used. Specimens from sites of the same kind may be combined if all sites are in one area, but specimens from different types of site (e.g. antenatal clinics, voluntary counselling and testing centres, sexually transmitted infection clinics) should not be combined, nor should specimens from different areas of a country. In countries where the risks of transmitted HIVDR may vary between HIV exposure risk groups, initial surveys should focus on the group with the highest risk.

Specific public health actions are recommended on the basis of the prevalence category for resistance to the drugs and drug categories. The results can contribute to decision-making about optimal ART regimens and prevention strategies based on the use of ART for pre-exposure and post-exposure prophylaxis, and about the prevention of mother-to-child transmission of HIV.

Monitoring of HIVDR emerging in treated populations at sentinel ART sites, and evaluation of related ART programme factors

The purpose of sentinel HIVDR monitoring is to evaluate the success of ART programmes in minimizing the emergence of HIVDR in the first year of ART, and to evaluate ART programme factors associated with HIVDR prevention. WHO recommends that sentinel ART sites be selected to represent the main clinic types in a given country with respect to geography, resources available, populations treated and regimens used. The cohort-based evaluation methodology is designed to be incorporated into the routine functioning of ART sites, with minimum data collection and genotyping of remnant specimens collected for routine clinical purposes.

A cohort of patients beginning first-line ART is evaluated at baseline and after 12 months, or at an end-point occurring earlier than 12 months. An effective sample size of 96 is included at each sentinel site. Because individuals beginning first-line ART in resource-limited settings may have ARV drug experience or transmitted resistance, the evaluation includes a baseline sequence of the relevant regions of the HIV *pol* gene and a history of ARV use, as well as recording initial regimens and any changes. At the time of switching to a second-line regimen or at 12 months for patients still on a first-line regimen (including substitutions), blood is collected for viral load testing and HIVDR genotyping. Other end-points may be determined by loss to follow-up, death, cessation of ART or transfer from one ART clinic to another. Since the HIVDR status of persons who have died or been transferred cannot be assessed, the corresponding data are not represented in the denominator and the numerator. For all evaluated individuals, standardized adherence measures and the regularity of both appointment- keeping and ARV drug pick-up are recorded. At the ART site level the continuity of drug supply is assessed.

The absence of HIVDR is defined as a suppressed viral load at the time of the second blood sampling; if plasma viral load is detected, patterns of resistance are analysed. Factors potentially associated with a lack of HIVDR prevention are recorded and analysed along with the outcomes. These factors include previous ARV exposure, irregularities in appointment-keeping or drug pick-

up, ARV prescribing practices, and a lack of drug supply continuity at the site in question. The association between patterns of resistance mutations and HIV-1 subtype are also evaluated if the numbers are adequate. The results support recommendations for optimal first-line and second-line regimens, indications for the time of regimen switching on a population basis, and specific actions to improve outcomes at sentinel clinics.

HIVDR early warning indicators

WHO suggests that countries routinely measure relevant variables associated with HIVDR prevention, including prescribing practices, adherence, appointment-keeping and ARV drug pick-up by patients, and drug supply continuity. WHO and its WHO/HIVResNet collaborators offer technical assistance to Member States for the planning and implementation of HIVDR strategies. This includes HIVDR protocol development, HIVDR database development, laboratory assessment and accreditation for HIVDR genotyping, the analysis of HIVDR data and the production of national HIVDR reports.

19. FUTURE DIRECTIONS TO IMPROVE ACCESS TO TREATMENT IN RESOURCE-LIMITED SETTINGS

Considerable progress has been made in the past four years towards making ART scale-up in the developing world a reality. However, much remains to be done. For people on treatment we must strive to make its benefits durable and sustainable. For people not yet on treatment but requiring it, resources have to be mobilized and systems put in place so as to reach them. These resources will be threatened by the high cost of drugs needed for moving to second-line regimens or by the inclusion of new drugs in first-line regimens. Universal access may not become a reality unless barriers to accessing all needed drugs are appropriately addressed.

We also cannot rest with the current formulary of available drugs as toxicities and drug resistance will drive the need for new treatment options. Every possible effort should be made to decrease the prices of these drugs as well as to ensure the production and use of the most adapted formulations. Moreover, all necessary measures should be taken to accelerate registration on approval for these products by national drug regulatory agencies, including fast-track approval of those products already included in the WHO prequalification list, which is regularly updated.

There are immediate needs in the area of diagnostics. Making affordable and accurate CD4 cell counting widely available is a high priority. Simultaneously, the field needs to move towards the development and implementation of affordable viral load testing. CD4 and plasma HIV-1 RNA testing are not luxuries. They are important tools supporting the delivery of optimal care and, in the setting of the public health approach, are invaluable measures of programme monitoring and performance. Clinical and operational research studies are crucial for providing the information needed to inform programme managers and clinicians about the optimal approaches to treating and monitoring HIV infection in resource-limited settings.

We hope the present edition of the WHO ART guidelines for adults and adolescents will be of practical value to programme managers and carers today while helping to move the field forward to reach more people in the near future and continuing to improve the standard of care for millions of HIV-infected persons worldwide.

CLINICAL STAGE 1

Asymptomatic
Persistent generalized lymphadenopathy

CLINICAL STAGE 2

Unexplained[a] moderate weight loss (under 10% of presumed or measured body weight)[b]
Recurrent upper respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infection

CLINICAL STAGE 3

Unexplained[a] severe weight loss (over 10% of presumed or measured body weight)[b]
Unexplained[a] chronic diarrhoea for longer than one month
Unexplained[a] persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia, severe pelvic inflamatory disease)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained[a] anaemia (below 8 g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopenia (below 50 x 10^9 /l)

CLINICAL STAGE 4[c]
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (coccidiomycosis or histoplasmosis)
Recurrent septicaemia (including non-typhoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

a   Unexplained refers to where the condition is not explained by other conditions.

b   Assessment of body weight among pregnant woman needs to consider the expected weight gain of pregnancy.

c   Some additional specific conditions can also be included in regional classifications, such as the reactivation of American trypanosomiasis (meningoencephalitis and/or myocarditis) in the WHO Region of the Americas and penicilliosis in Asia.

Source: *Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance.* 2006 (in press).

Clinical event	Clinical diagnosis	Definitive diagnosis
CLINICAL STAGE 1		
Asymptomatic	No HIV-related symptoms reported and no signs on examination	Not applicable
Persistent generalized lymphadenopathy	Painless enlarged lymph nodes >1 cm, in two or more noncontiguous sites (excluding inguinal), in absence of known cause and persisting for three months or longer	Histology
CLINICAL STAGE 2		
Moderate unexplained weight loss (under 10% of body weight)	Reported unexplained weight loss. In pregnancy, failure to gain weight	Documented weight loss (under 10% of body weight)
Recurrent bacterial upper respiratory tract infections (current event plus one or more in last six months)	Symptoms complex, e.g. unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media), or tonsillopharyngitis without features of viral infection (e.g. coryza, cough)	Laboratory studies if available, e.g. culture of suitable body fluid
Herpes zoster	Painful vesicular rash in dermatomal distribution of a nerve supply does not cross midline	Clinical diagnosis
Angular cheilitis	Splits or cracks at the angle of the mouth not attributable to iron or vitamin deficiency, and usually responding to antifungal treatment	Clinical diagnosis
Recurrent oral ulceration (two or more episodes in last six months)	Aphthous ulceration, typically painful with a halo of inflammation and a yellow-grey pseudomembrane	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Papular pruritic eruption	Papular pruritic lesions, often with marked postinflammatory pigmentation	Clinical diagnosis
Seborrhoeic dermatitis	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin)	Clinical diagnosis
Fungal nail infection	Paronychia (painful red and swollen nail bed) or onycholysis (separation of nail from nail bed) of the fingernails (white discolouration, especially involving proximal part of nail plate, with thickening and separation of nail from nail bed)	Fungal culture of nail / nail plate material
CLINICAL STAGE 3		
Severe unexplained weight loss (more than 10% of body weight)	Unexplained reported weight loss (over 10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index below 18.5. In pregnancy, weight loss may be masked.	Documented loss of more than 10% of body weight
Unexplained chronic diarrhoea for longer than one month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month	Three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained persistent fever (intermittent or constant and lasting for longer than one month)	Reports of fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarials, without other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Documented fever exceeding 37.5 °C with negative blood culture, negative Ziehl-Nielsen (ZN) stain, negative malaria slide, normal or unchanged chest X-ray (CXR) and no other obvious focus of infection
Persistent oral candidiasis	Persistent or recurring creamy white curd-like plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form)	Clinical diagnosis
Oral hairy leukoplakia	Fine white small linear or corrugated lesions on lateral borders of the tongue, which do not scrape off	Clinical diagnosis
Pulmonary tuberculosis (current)	Chronic symptoms (lasting at least two to three weeks): cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats, PLUS either positive sputum smear OR negative sputum smear AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, cavitation, pulmonary fibrosis and shrinkage). No evidence of extrapulmonary disease.	Isolation of *M. tuberculosis* on sputum culture or histology of lung biopsy (together with compatible symptoms)

Clinical event	Clinical diagnosis	Definitive diagnosis
Severe bacterial infection (e. g. pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)	Fever accompanied by specific symptoms or signs that localize infection, and response to appropriate antibiotic	Isolation of bacteria from appropriate clinical specimens (usually sterile sites)
Acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	Clinical diagnosis
Unexplained anaemia (below 8g/dl), neutropenia (below 0.5×10^9/l) or chronic (more than one month) thrombocytopenia (under 50×10^9/l)	No presumptive clinical diagnosis	Diagnosed on laboratory testing and not explained by other non-HIV conditions. Not responding to standard therapy with haematinics, antimalarials or anthelmintics as outlined in relevant national treatment guidelines, WHO IMCI guidelines or other relevant guidelines.
CLINICAL STAGE 4		
HIV wasting syndrome	Unexplained involuntary weight loss (over 10% of body weight) with obvious wasting or body mass index below 18.5 PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarials. Malaria must be excluded in malarious areas.	Documented weight loss (over 10% of body weight) plus two or more unformed stools negative for pathogens or documented temperature exceeding 37.6 °C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR

Clinical event	Clinical diagnosis	Definitive diagnosis
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND CXR evidence of diffuse bilateral interstitial infiltrates, AND no evidence of bacterial pneumonia, bilateral crepitations on auscultation with or without reduced air entry.	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage (BAL), or histology of lung tissue.
Recurrent bacterial pneumonia (this episode plus one or more episodes in last six months)	Current episode plus one or more episodes in last six months. Acute onset (under two weeks) of symptoms (e.g. fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or CXR. Response to antibiotics.	Positive culture or antigen test of a compatible organism
Chronic herpes simplex virus (HSV) infection (orolabial, genital or anorectal) of more than one month, or visceral of any duration	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrent HSV infection and reported for more than one month. History of previous episodes. Visceral HSV requires definitive diagnosis.	Positive culture or DNA (by PCR) of HSV or compatible cytology/histology
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/histology

Clinical event	Clinical diagnosis	Definitive diagnosis
Extrapulmonary tuberculosis	Systemic illness (e.g. fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated TB varies by site: pleural, pericardial, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or osteitis. Discrete peripheral lymph node *M. tuberculosis* infection is considered a less severe form of extrapulmonary tuberculosis.	*M. tuberculosis* isolation or compatible histology from appropriate site OR radiological evidence of miliary TB (diffuse uniformly distributed small miliary shadows or micronodules on CXR.
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat patches with a pink or blood-bruise colour, skin lesions that usually develop into violaceous plaques or nodules.	Macroscopic appearance at endoscopy or bronchoscopy, or by histology.
Cytomegalovirus disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Compatible histology or CMV demonstrated in CSF by culture or DNA (by PCR)
Central nervous system toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within ten days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single/multiple intracranial mass lesion on neuroimaging (CT or MRI)

Clinical event	Clinical diagnosis	Definitive diagnosis
HIV encephalopathy	Clinical finding of disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition, other than HIV infection, which might explain the findings	Diagnosis of exclusion, and, if available, neuroimaging (CT or MRI)
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasingly severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy	Isolation of *Cryptococcus neoformans* from extrapulmonary site or positive cryptococcal antigen test (CRAG) on CSF/blood
Disseminated non-tuberculous mycobacteria infection	No presumptive clinical diagnosis	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung
Progressive multifocal leukoencephalopathy (PML)	No presumptive clinical diagnosis	Progressive neurological disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC (JCV) PCR on CSF
Chronic cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool.
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*

Clinical event	Clinical diagnosis	Definitive diagnosis
Disseminated mycosis (coccidiomycosis or histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent septicaemia (including non-typhoidal salmonella)	No presumptive clinical diagnosis	Blood culture
Lymphoma (cerebral or B cell non-Hodgkin) or other solid HIV- associated tumours	No presumptive clinical diagnosis	Histology of relevant specimen or, for CNS tumours, neuroimaging techniques
Invasive cervical carcinoma	No presumptive clinical diagnosis	Histology or cytology.
Atypical disseminated leishmaniasis	No presumptive clinical diagnosis	Histology (amastigotes visualized) or culture from any appropriate clinical specimen
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance, 2006 (in press).

Generic Name	Dose
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Zidovudine (AZT)	250−300 mg twice daily
Emtricitabine (FTC)	200 mg once daily
Didanosine (ddI) Buffered tablets or enteric-coated (EC) capsules [a]	>60 kg: 400 mg once daily <60 kg: 250 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T) [b]	>60 kg: 40 mg twice daily <60 kg: 30 mg twice daily
NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	
Tenofovir	300 mg once daily
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
Efavirenz (EFV)	600 mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
PROTEASES INHIBITORS	
Atazanavir + ritonavir (ATV/r)	300 mg +100 mg once daily
Fos-amprenavir + ritonavir (FPV/r)	700mg + 100 mg twice daily
Indinavir + ritonavir (IDV/r) [c]	800 mg + 100 mg twice daily

Generic Name	Dose	
PROTEASE INHIBITORS		
Lopinavir/ritonavir (LPV/r) [d]	**Capsules** Lopinavir 133.3 mg / ritonavir 33.3 mg	• Three capsules twice daily (400/100 mg twice daily) • Four capsules twice daily when combined with EFV or NVP (533/133.33 mg twice daily)
	Tablets (heat-stable formulation) Lopinavir 200 mg / ritonavir 50 mg	**Treatment-naive patients** • Two tablets twice daily irrespective of coadministration with EFV or NVP (400/100 mg twice daily)
		Treatment-experienced patients • Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily)
Nelfinavir (NFV)	1250 mg twice daily	
Saquinavir + ritonavir (SQV/r) [d]	1000 mg + 100 mg twice daily	

a   ddI dose should be adjusted when coadministered with tenofovir. If weight is above 60 kg the recommended dose is 250 mg once daily. If weight is below 60 kg there are no data on which to base a recommendation (some preliminary pK studies suggest 125–200 mg once daily).[193] Buffered ddI should be taken on an empty stomach.

b   Some experts recommend d4T at 30 mg for all patients irrespective of body weight.

c   Other dose regimens in clinical use are 600 mg + 100 mg twice daily[194] and 400 mg + 100 mg twice daily.[195, 196, 197]

d   See Section 12 for TB-specific dose modifications of lopinavir/r and saquinavir + ritonavir.

Generic name	Storage requirements
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
Abacavir (ABC)	Room temperature
Zidovudine (AZT)	Room temperature
Didanosine (ddI)	Room temperature for tablets and capsules Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated
Emtricatabine (FTC)	Room temperature
Lamivudine (3TC)	Room temperature
Stavudine (d4T)	Room temperature. After reconstitution, oral solution should be kept refrigerated, in which case it is stable for 30 days
Stavudine (d4T) + lamivudine (3TC) + nevirapine (NVP)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + abacavir (ABC)	Room temperature
Zidovudine (AZT) + lamivudine (3TC) + nevirapine (NVP)	Room temperature
Tenofovir (TDF)	Room temperature
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
Efavirenz (EFV)	Room temperature
Nevirapine (NVP)	Room temperature

Generic name	Storage requirements
PROTEASE INHIBITORS	
Atazanavir (ATV)	Room temperature
Indinavir (IDV)	Room temperature
Fos-amprenavir (FPV)	Room temperature
Lopinavir/ritonavir (LPV/r) capsules	Refrigerate for long-term storage. Stable for 30 days at room temperature
Lopinavir/ritonavir (LPV/r) heat-stable tablets	Room temperature
Nelfinavir (NFV)	Room temperature
Ritonavir (RTV)	Refrigerate capsules until dispensed. Stable at room temperature for 30 days. Room temperature for oral solution (do not refrigerate).
Saquinavir hard gel capsules (SQV$_{hgc}$)	Room temperature
Room temperature is defined as 15−30 ºC. Refrigeration is defined as 2−8 ºC.	

ANNEX 5. DRUGS THAT INTERACT WITH ANTIRETROVIRALS

ARVs	NVP	EFV	
ANTIMYCOBACTERIUM			
Rifampicin	↓ NVP level by 20% to 58%. Virological consequences are uncertain; potential for additive hepatotoxicity exists. Coadministration is recommended only if done with careful monitoring.	↓ EFV level by 25%	
Rifabutin	Levels: NVP ↓ 16%. No dose adjustment.	Levels: EFV unchanged. Rifabutin ↓ 35%. Dose: ↑ rifabutin dose to 450−600 mg once daily or 600 mg three times a week. EFV: standard.	
Clarithromycin	None	↓ clarithromycin by 39%. Monitor for efficacy or use alternative drugs.	
ANTIFUNGAL			
Ketoconazole	↑ ketoconazole level by 63%. ↑ NVP level by 15−30%. Do not recommend coadministration.	No significant changes in ketoconazole or EFV levels	

	LPV/r	NFV	SQV
	↓ LPV AUC by 75%. Should not be coadministered.	↓ NFV level by 82%. Should not be coadministered.	↓ SQV level by 84%. Severe liver impairment reported with coadministration. Should not be coadministered.
	Levels: rifabutin AUC ↑ threefold. Decrease rifabutin dose to 150 mg once daily or three times a week. LPV/r: standard.	Levels: NFV ↓ 82%. Should not be coadministered.	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150 mg once daily or three times a week.
	↑ clarithromycin AUC by 75%. Adjust clarithromycin dose if renal impairment.	No data	Without RTV, ↑ clarithromycin level by 45%, ↑ SQV level by 177%. RTV can ↑ clarithromycin level by 75%. No clarithromycin dose adjustment needed for unboosted SQV. For boosted SQV if renal impairment – no data.
	ANTIFUNGAL		
	↑ LPV AUC. ↑ ketoconazole level threefold. Do not exceed 200 mg/day ketoconazole.	No dose adjustment necessary	↑ SQV level threefold. No dose adjustment necessary if given unboosted. For RTV-boosted SQV – no data (RTV treatment dose can increase ketoconazole level threefold).

ARVs	NVP	EFV	
Fluconazole	↑ NVP Cmax, AUC, Cmin by 100%. No change in fluconazole level. Possible increase in hepatotoxicity with coadministration requiring monitoring of NVP toxicity.	No data	
Intraconazole	No data	No data	
ORAL CONTRACEPTIVES			
Ethinyl estradiol	↓ ethinyl estradiol by 20%. Use alternative or additional methods.	↑ ethinyl estradiol by 37%. Use alternative or additional methods.	
ANTICONVULSANTS			
Carbamazepine Phenytoin	Use with caution. One case report showed low EFV concentrations with phenytoin.	Unknown. Use with caution.	

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	LPV/r	NFV	SQV
	No data	No data	No data
	↑ intraconazole level. Do not exceed 200 mg/day intraconazole.	No data but potential for bidirectional inhibition. Monitor toxicities.	Bidirectional interaction has been observed. It may be necessary to decrease intraconazole dose. Consider monitoring SQV level (especially if given unboosted with RTV).
	↓ ethinyl estradiol level by 42%. Use alternative or additional methods.	↓ norethindrone level by 18%. ↓ ethinyl estradiol level by 47%.	No data for unboosted SQV. RTV treatment dose can ↓ level of ethinyl estradiol by 41%.
	Many possible interactions. Carbamazepine: ↑ levels when coadministered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓ levels of LPV and RTV, and ↓ levels of phenytoin when administered together. Avoid concomitant use or monitor LPV level.	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virological response.	Unknown, but may markedly reduce SQV levels. Monitor anticonvulsant levels and consider obtaining SQV level.

ARVs	NVP	EFV	
OPIOID SUBSTITUTION TREATMENT			
Methadone	Levels: NVP unchanged. Methadone ↓ significantly. Opiate withdrawal common when this combination is used. Increased methadone dose often necessary. Titrate methadone dose to effect.	Levels: methadone ↓ 60%. Opiate withdrawal common, increase in methadone dose often necessary. Titrate methadone dose to effect.	
Buprenorphine	Not studied	Buprenorphine levels ↓ 50% but no withdrawals reported. No dose adjustment is recommended.	
LIPID-LOWERING AGENTS			
Simvastatin, Lovastatin	No data	↓ simvastatin level by 58%. EFV level unchanged. Adjust simvastatin dose according to lipid response; not to exceed the maximum recommended dose.	
Atorvastatin	No data	↓ atorvastatin AUC by 43%. EFV level unchanged. Adjust atorvastatin dose according to lipid response; not to exceed maximum recommended dose.	
Pravastatin	No data	No data	

	LPV/r	NFV	SQV
	Methadone AUC ↓ 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May require increase in methadone dose.	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require increase in methadone dose.	Methadone AUC ↓ 20% when coadministered with SQV/RTV 400/400 mg b.d. No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.
	No significant interactions	No significant interactions	No significant interactions
	Potential large ↑ statin level. Avoid concomitant use.	↑ simvastatin AUC by 505%. Potential large ↑ lovastatin AUC. Avoid concomitant use.	Potential large ↑ statin level. Avoid concomitant use.
	↑ atorvastatin AUC 5.88 fold. Use lowest possible starting dose with careful monitoring.	↑ atorvastatin AUC 74%. Use lowest possible starting dose with careful monitoring.	↑ atorvastatin level by 450% when used as SQV/RTV. Use lowest possible starting dose with careful monitoring.
	↑ pravastatin AUC 33%. No dose adjustment needed.	No data	↓ pravastatin level by 50%. No dose adjustment needed.

ARVs	NVP	EFV	
ANTICONVULSANTS			
Carbamazepine, Phenobarbital, Phenytoin	Unknown. Use with caution. Monitor anticonvulsant levels.	Use with caution. One case report showed low EFV levels with phenytoin. Monitor anticonvulsant and EFV levels.	
Proton pump inhibitors. All the PIs and EFV can increase levels of cisapride and non-sedating antihistamines (aztemizole, terfenedine), which can cause cardiac toxicity. Coadministration is not recommended.			

	LPV/r	NFV	SQV
	↑ carbamazepine from RTV. Both phenytoin and LPV/r levels ↓. For all, avoid concomitant use or monitor LPV/anticonvulsant levels.	Unknown but may decrease NFV level substantially. Monitor NFV/anticonvulsant levels.	Unknown for unboosted SQV but may markedly ↓ SQV level. Monitor SQV/anticonvulsant levels.
	Proton pump inhibitors. All the PIs and EFV can increase levels of cisapride and non-sedating antihistamines (aztemizole, terfenedine), which can cause cardiac toxicity. Coadministration is not recommended.		

AUC: area under the curve.

Cmax: maximum concentration.

Cmin: minimum concentration.

Note: Concomitant use of fluticasone with RTV results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone with RTV or any RTV-boosted PI regimen is not recommended unless the potential benefit outweighs the risk of systemic corticosteroid side-effects.

(Adapted from *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents.* 4 May 2006. - www.aidsinfo.nih.gov).

Diagnosis and monitoring laboratory tests		Primary care level	District level	Regional/ referral level
HIV antibody testing [a]		✓	✓	✓
HIV virological diagnostic testing [b]		-	+	✓
Haemoglobin [c]		+	✓	✓
WBC and differential		-	✓	✓
CD4 (absolute count and %)		-	✓	✓
Pregnancy testing [d]		+	✓	✓
ALT		-	✓	✓
Full chemistry (including but not restricted to: liver enzymes, renal function, glucose, lipids, amylase and serum electrolytes)		-	-	✓
Diagnostic tests for treatable coinfections and major HIV-related opportunistic diseases	Basic microscopy for TB and malaria (sputum smear for TB and blood film for malaria diagnosis) [e]	+	✓	✓
	Full cerebrospinal fluid aspirate examination (microscopy, India ink, Gram stain, Ziehl-Nielsen); syphilis and other STI diagnostic tests	-	✓	✓
	Diagnostic tests for hepatitis B, hepatitis C serology, bacterial microbiology and cultures and diagnostic tests and procedures for PCP, *Cryptococcus*, toxoplasmosis and other major OIs	-	+	✓
HIV viral load measurement [f]		-	-	+

✓　Essential test.

+　Desirable but non-essential test.

-　Non-essential test.

a　Rapid tests are recommended at primary level and conventional methodologies can be used at district and regional/central levels.

b　Virological testing for establishing HIV diagnosis in infants and children aged under 18 months can be performed using dried blood spots.

c　Should be available if AZT is being considered for use.

d　Should be available if EFV is being considered for use.

e　Referral if microscopy is not available.

f　Viral load measurement is not currently recommended for decision-making on initiation or regular monitoring of ART in resource-limited settings. Tests for HIV-RNA viral load can also be used to diagnose HIV infection.

ANNEX 7. SEVERITY GRADING OF SELECTED CLINICAL AND LABORATORY TOXICITIES

(Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, USA − modified.)

For abnormalities NOT found elsewhere in the toxicity table use the scale below to estimate grades of toxicity.

GRADE 1   Transient or mild discomfort; no limitation of activity; no medical intervention/therapy required.

GRADE 2   Mild to moderate limitation of activity; some assistance may be needed; no or minimal medical intervention/therapy required.

GRADE 3   Marked limitation of activity; some assistance usually required; medical intervention/therapy required; hospitalization possible.

GRADE 4   Extreme limitation of activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care.

Haematology	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin	8.0 − 9.4 g/dl **OR** 80 − 94 g/l **OR** 4.93 − 5.83 mmol/l	7.0 − 7.9 g/dl **OR** 70 − 79 g/l **OR** 4.31 − 4.92 mmol/l	6.5 − 6.9 g/dl **OR** 65 − 69 g/l **OR** 4.03 − 4.30 mmol/l	<6.5 g/dl **OR** <65 g/l **OR** <4.03 mmol/l
Absolute neutrophil count	1000 −1500/mm^3 **OR** 1.0 − 1.5/G/l*	750 − 999/mm^3 **OR** 0.75 − 0.99/G/l*	500 − 749/mm^3 **OR** 0.5 − 0.749/G/l*	<500/mm^3 **OR** <0.5/G/l*
Platelets	75000 − 99000/mm^3 **OR** 75 − 99/G/l*	50000 − 74999/mm^3 **OR** 50 − 74.9/G/l*	20000 − 49999/mm^3 **OR** 20 − 49.9/G/l*	<20000/mm^3 **OR** <20/G/l*
Chemistries	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
SODIUM				
Hyponatraemia	130 − 135 meq/l **OR** 130 − 135 mmol/l	123 − 129 meq/l **OR** 123 − 129 mmol/l	116 − 122 meq/l **OR** 116 − 122 mmol/l	<116 meq/l **OR** <116 mmol/l
Hypernatraemia	146 − 150 meq/l **OR** 146 − 150 mmol/l	151 − 157 meq/l **OR** 151 − 157 mmol/l	158 − 165 meq/l **OR** 158 − 165 mmol/l	>165 meq/l **OR** >165 mmol/l

Chemistries	Grade 1	Grade 2	Grade 3	Grade 4
POTASSIUM				
Hyperkalaemia	5.6 − 6.0 meq/l **OR** 5.6 − 6.0 mmol/l	6.1 − 6.5 meq/l **OR** 6.1 − 6.5 mmol/l	6.6 − 7.0 meq/l **OR** 6.6 − 7.0 mmol/l	>7.0 meq/l **OR** >7.0 mmol/l
Hypokalaemia	3.0 − 3.4 meq/l **OR** 3.0 − 3.4 mmol/l	2.5 − 2.9 meq/l **OR** 2.5 − 2.9 mmol/l	2.0 − 2.4 meq/l **OR** 2.0 − 2.4 mmol/l	<2.0 meq/l **OR** <2.0 mmol/l
BILIRUBIN				
Hyperbilirubin-aemia	>1.0 − 1.5 x ULN	>1.5 − 2.5 x ULN	>2.5 − 5 x ULN	>5 x ULN
GLUCOSE				
Hypoglycaemia	55 − 64 mg/dl **OR** 3.01 − 3.55 mmol/l	40 − 54 mg/dl **OR** 2.19 − 3.00 mmol/l	30 − 39 mg/dl **OR** 1.67 − 2.18 mmol/l	<30 mg/dl **OR** <1.67 mmol/l
Hyperglycaemia (nonfasting and no prior diabetes)	116 − 160 mg/dl **OR** 6.44 − 8.90 mmol/l	161 − 250 mg/dl **OR** 8.91 − 13.88 mmol/l	251 − 500 mg/dl **OR** 13.89 − 27.76 mmol/l	>500 mg/dl **OR** >27.76 mmol/l
Triglycerides	200 – 399 mg/dl **OR** 2.25 - 4.51 mmol/l	400 − 750 mg/dl **OR** 4.52 − 8.47 mmol/l	751 − 1200 mg/dl **OR** 8.48 − 13.55 mmol/l	>1200 mg/dl **OR** >13.55 mmol/l
Creatinine	>1.0 − 1.5 x ULN	>1.5 − 3.0 x ULN	>3.0 − 6.0 x ULN	>6.0 x ULN
TRANSAMINASES				
AST (SGOT)	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
GGT	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN
Alkaline phosphatase	1.25 − 2.5 x ULN	>2.5 − 5.0 x ULN	>5.0 − 10.0 x ULN	>10.0 x ULN

Chemistries	Grade 1	Grade 2	Grade 3	Grade 4
TRANSAMINASES				
Pancreatic enzymes				
Amylase	>1.0 − 1.5 x ULN	>1.5 − 2.0 x ULN	>2.0 − 5.0 x ULN	>5.0 x ULN
Pancreatic amylase	>1.0 − 1.5 x ULN	>1.5 − 2.0 x ULN	>2.0 − 5.0 x ULN	>5.0 x ULN
Lipase	>1.0 − 1.5 x ULN	>1.5 − 2.0 x ULN	>2.0 − 5.0 x ULN	>5.0 x ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life- threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Gastrointestinal	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	Mild **OR** transient; reasonable intake maintained	Moderate discomfort **OR** intake decreased for <3 days	Severe discomfort **OR** minimal intake for ≥3 days	Hospitalization required
Vomiting	Mild **OR** transient; 2−3 episodes per day **OR** mild vomiting lasting <1 week	Moderate **OR** persistent; 4−5 episodes per day **OR** vomiting lasting ≥1 week	Severe vomiting of all foods/fluids in 24 hours **OR** orthostatic hypotension **OR** intravenous Rx required	Hypotensive shock **OR** hospitalization for intravenous Rx required
Diarrhoea	Mild **OR** transient; 3−4 loose stools per day **OR** mild diarrhoea lasting <1 week	Moderate **OR** persistent; 5−7 loose stools per day **OR** diarrhoea lasting ≥1 week	Bloody diarrhoea **OR** orthostatic hypotension **OR** >7 loose stools/day **OR** intravenous Rx required	Hypotensive shock **OR** hospitalization required

Respiratory	Grade 1	Grade 2	Grade 3	Grade 4
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O^2 therapy
Urinalysis	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria				
Spot urine	1+	2+ or 3+	4+	Nephrotic syndrome
24-hour urine	200 mg to 1 g loss/day **OR** <0.3% **OR** <3 g/l	1 g to 2 g loss/day **OR** 0.3% to 1.0% **OR** 3 g to 10 g/l	2 g to 3.5 g loss/day **OR** >1.0% **OR** >10 g/l	Nephrotic syndrome **OR** >3.5 g loss/day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
Miscellaneous	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever (oral, >12 hours)	37.7 − 38.5 ºC **OR** 100.0 − 101.5 ºF	38.6 − 39.5 ºC **OR** 101.6 − 102.9 ºF	39.6 − 40.5ºC **OR** 103 − 105 ºF	>40.5 ºC **OR** >105 ºF for ≥12 continuous hours
Headache	Mild; no Rx required	Moderate **OR** non-narcotic analgesia Rx	Severe **OR** responds to initial narcotic Rx	Intractable
Rash hypersesnitivity	Erythema, pruritus	Diffuse maculopapular rash **OR** dry desquamation	Vesiculation **OR** moist desquamation **OR** ulceration	**ANY ONE OF**: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, exfoliative dermatitis

Miscellaneous	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25−50%	Normal activity reduced by >50%; cannot work	Unable to care for self

Adverse effect	Major ARVs	Recommendations
Acute pancreatitis	d4T and ddl	Discontinue ART. Give supportive treatment and conduct laboratory monitoring. Resume ART with an NRTI with low pancreatic toxicity risk. AZT, ABC, TDF and 3TC are less likely to cause this type of toxicity.
Diarrhoea	ddl (buffered formulation), NVF, LPV/r and SQV/r	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Drug eruptions (mild to severe, including Stevens-Johnson syndrome or toxic epidermal necrolysis)	NVP, EFV (rarely)	In very mild cases, antihistamines and strict observation; there may be regression without need to change ART. If mild/moderate rash, non-progressing and without mucosal involvement or systemic signs, consider a single NNRTI substitution (i.e. from NVP to EFV). In moderate and severe cases, discontinue ART and give supportive treatment. After resolution, resume ART with three NRTIs or two NRTIs + PIs.
Dyslipidaemia, insulin resistance and hyperglycaemia	PIs	Consider replacing the suspected PI by drugs with less risk of metabolic toxicity (e.g. NFV). Adequate diet, physical exercise and antilipaemic drugs should be considered.
GI intolerance, with taste changes, nausea, vomiting, abdominal pain and diarrhoea.	All ARVs (less frequent with d4T, 3TC, FTC and ABC)	Usually self-limited, without need to discontinue ART. Symptomatic treatment should be offered.
Haematological toxicities (particularly anaemia and leukopenia)	AZT	If severe (Hg <6.5 g% and/or ANC <500 cells/mm^3), replace by an ARV with minimal or no bone marrow toxicity (e.g. d4T, ABC or TDF) and consider blood transfusion.

Adverse effect	Major ARVs	Recommendations
Hepatitis	All ARVs (particularly with NVP and ritonavir-boosted PIs)	Intense elevations of ALT associated with clinical features have been described with NVP; however, changes of varying intensity may be observed with all ARVs, mediated by different mechanisms. If ALT is at more than five times the basal level, discontinue ART and monitor. After resolution, replace the drug most likely associated with the condition.
Hyperbilirubinaemia (indirect)	ATV	Generally asymptomatic but can cause scleral icterus (without ALT elevations). Replace ATV with other PI.
Hypersensitivity reaction with respiratory symptoms,, fever and without mucosal involvement.	ABC	Discontinue ABC and **do not restart**. Symptomatic treatment. Re-exposure may lead to a severe and potentially life-threatening reaction.
Lactic acidosis	All NRTIs (particularly d4T and ddI)	Discontinue ART and give supportive treatment. After clinical resolution, resume ART, replacing the offending NRTI. ABC, TDF and 3TC are less likely to cause this type of toxicity.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T)	Early replacement of the suspected ARV drug (e.g. d4T for TDF or ABC). Consider aesthetic treatment and physical exercises.
Neuropsychiatric changes (sleep disturbances; depression; behavioural, concentration and personality changes)	EFV	Usually self-limited, without the need to discontinue ART. Symptomatic treatment if required. If a previous psychiatric disturbance has occurred there is a higher risk of a more severe reaction. Effects may be enhanced by alcohol and other psychoactive drugs.

Adverse effect	Major ARVs	Recommendations
Renal toxicity (nephrolithiasis)	IDV	If using IDV, interrupt it and offer hydration, laboratory monitoring and symptomatic treatment (50% recurrence rate). Consider replacing IDV with another PI.
Renal toxicity (renal tubular dysfunction)	TDF	Discontinue TDF and give supportive treatment. After clinical resolution, resume ART, replacing the offending drug.
Peripheral neuropathy	d4T and ddl	Consider replacement by an NRTI with minimal or no neurotoxicity (AZT, TDF or ABC). Symptomatic treatment should be considered.

Stage	Female				
	Age range (years)	Breast growth	Pubic hair growth	Other changes	
I	0 − 15	Pre-adolescent	None	Pre-adolescent	
II	8 − 15	Breast budding (thelarche); areolar hyperplasia with small amount of breast tissue	Long, downy pubic hair near the labia, often appearing simultaneously with breast budding or several weeks or months later	Peak growth velocity often occurs soon after stage II	
III	10 − 15	Further enlargement of breast tissue and areola, with no separation of their contours	Increase in amount and pigmentation of hair	Menarche occurs in 2% of girls late in stage III	
IV	10 − 17	Separation of contours; areola and nipple form secondary mound above breast tissue	Adult in type but not in distribution	Menarche occurs in most girls in stage IV, 1 − 3 years after thelarche	
V	12.5 − 18	Large breast with single contour	Adult in distribution	Menarche occurs in 10% of girls in stage V	

	Male				
	Age range (years)	Testes growth	Penis growth	Pubic hair growth	Other changes
	0 −15	Pre-adolescent (≤2.5 cm)	Pre-adolescent	None	Pre-adolescent
	10 − 15	Enlargement of testes, pigmentation of scrotal sac	Minimal or no enlargement	Long, downy hair, often appearing several months after testicular growth; variable pattern noted with pubarche	Not applicable
	10.5 − 16.5	Further enlargement	Significant enlargement, especially in diameter	Increase in amount; curling	Not applicable
	Variable: 12 − 17	Further enlargement	Further enlargement, especially in diameter	Adult in type but not in distribution	Axillary hair and some facial hair develop
	13 − 18	Adult in size	Adult in size	Adult in distribution (medial aspects of thighs; linea alba)	Body hair continues to grow and muscles continue to increase in size for several months to years; 20% of boys reach peak growth velocity during this period

Source: Adapted from reference 198

Three-drug fixed-dose combinations	AZT + 3TC + ABC (co-formulation and co-blister)
	AZT + 3TC +NVP (co-formulation and co-blister)
	AZT + 3TC + EFV (co-blister)
	d4T + 3TC + NVP (co-formulation)
	TDF + FTC + EFV (co-formulation)
Two-drug fixed-dose combinations	ABC + 3TC (co-formulation)
	AZT + 3TC (co-formulation)
	d4T + 3TC (co-formulation)
	LPV/r (co-formulation)
	TDF + FTC (co-formulation)

a   Co-formulations are based on the principle of inclusion of two or more active pharmacological products in the same capsule, tablet or solution.

b   Blister packs is defined a plastic or aluminium blister containing two or more capsules or tablets.

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ANTIRETROVIRAL THERAPY FOR HIV INFECTION
IN ADULTS AND ADOLESCENTS

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