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

2010 revision

World Health Organization

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1. ACRONYMS AND ABBREVIATIONS

3TC	lamivudine
AB	antibody
ABC	abacavir
ACTG	AIDS Clinical Trials Group
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	antenatal clinic
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AZT	zidovudine (also known as ZDV)
BID	twice daily
BMI	body mass index
bPI	boosted protease inhibitor
CD4 cell	T-lymphocyte bearing CD4 receptor
CEM	cohort event monitoring
CMV	cytomegalovirus
CNS	central nervous system
CXR	chest X-ray
d4T	stavudine
DART	Development of Antiretroviral Therapy (in Africa)
DBS	dried blood spot
ddI	didanosine
DNA	deoxyribonucleic acid
DRV	darunavir
EC	enteric-coated
EFV	efavirenz
EIA	enzyme immunoassay
ETV	etravirine
EPTB	extrapulmonary tuberculosis
FBC	full blood count
FDC	fixed-dose combination
FPV	fos-amprenavir
FTC	emtricitabine

GDG	Guidelines Development Group
GI	gastrointestinal
GNP+	Global Network of People Living with HIV
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIVDR	HIV drug resistance
HIVRNA	human immunodeficiency virus ribonucleic acid
HSV	herpes simplex virus
ICW	International Community of Women Living with HIV/AIDS
IDU	injecting drug user
IDV	indinavir
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
ITCP	International Treatment Preparedness coalition
LPV	lopinavir
LPV/r	lopinavir/ritonavir
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
OBR	optimized background regimen
OI	opportunistic infection
OST	opioid substitution treatment
PCP	*Pneumocystis jiroveci* pneumonia
PEPFAR	President's Emergency Plan for AIDS Relief
PETRA	Perinatal Transmission Study
PGL	persistent generalized lymphadenopathy
PI	protease inhibitor
PLHIV	people living with HIV

PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
/r	low-dose ritonavir
RAL	raltegravir
RBV	ribavirin
RCT	randomized clinical trial
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reverse transcriptase inhibitor
RTV	ritonavir
Sd-NVP	single-dose nevirapine
SJS	Stevens-Johnson syndrome
SQV	saquinavir
STI	structured treatment interruption
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEN	toxic epidermal necrolysis
TLC	total lymphocyte count
VL	viral load
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
WBC	white blood cell count
WHO	World Health Organization

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3. EXECUTIVE SUMMARY

Since the publication in 2006 of *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach*, new evidence has emerged on when to initiate ART, optimal ART regimens, the management of HIV coinfection with tuberculosis and chronic viral hepatitis and the management of ART failure. This evidence formed the basis for the recommendations contained in the 2010 update, which outlines a public health approach to the delivery of ART for adults and adolescents in settings with limited health systems capacity and resources. The recommendations were based on the preparation GRADE evidence profiles, systematic and targeted reviews, risk-benefit analyses, consultations with PLHIV, technical reports, and assessments of impact, feasibility and cost.

This guideline revision was conducted in accordance with procedures outlined by the *WHO Guidelines Review Committee* and is based on the GRADE approach to evidence review. The process involved four separate working groups: the *Internal WHO ART Guideline Working Group,* the *ART Guideline Drafting Group*, the external *ART Peer Review Panel* and the full *ART Guideline Review Committee*.

The consensus recommendations, which emerged from consultations of the working groups, encourage earlier HIV diagnosis and earlier antiretroviral treatment, and promote the use of less toxic regimens and more strategic laboratory monitoring. The guidelines identify the most potent, effective and feasible first-line, second-line and subsequent treatment regimens, applicable to the majority of populations, the optimal timing of ART initiation and improved criteria for ART switching, and introduce the concept of third-line antiretroviral regimens.

The primary audiences are national treatment advisory boards, partners implementing HIV care and treatment, and organizations providing technical and financial support to HIV care and treatment programmes in resource-limited settings.

It is critical that national ART programme and public health leaders consider these recommendations in the context of countries' HIV epidemics, the strengths and weaknesses of health systems, and the availability of financial, human and other essential resources. In adapting these guidelines, care must be exercised to avoid undermining current treatment programmes, to protect access for the most at-risk populations, to achieve the greatest impact for the greatest number of people and to ensure sustainability. It is similarly important to ensure that the adaptation of these guidelines do not stifle ongoing or planned research, since the new recommendations reflect the current state of knowledge and new information for sustainability and future modifications of existing guidelines will be needed.

4. BACKGROUND

WHO guidelines for ART for HIV infection in adults and adolescents were originally published in 2002, and were revised in 2003 and 2006. New evidence has emerged on when to initiate ART, optimal ART regimens, the management of HIV coinfection with tuberculosis and chronic viral hepatitis, and the management of ART failure. This evidence formed the basis for the new recommendations contained in the 2010 guidelines and summarized in the *Rapid advice: Antiretroviral therapy for HIV infection in adults and adolescents* (http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf). Consideration was given to the risks and benefits of implementing each recommendation, in addition to its acceptability, cost and feasibility. The guidelines incorporate the best available evidence within a framework that emphasizes the public health approach to the scaling up of quality HIV care and treatment.(*1*)

The consensus recommendations encourage earlier diagnosis and earlier treatment, and promote the use of less toxic regimens and more strategic laboratory monitoring. It is critical that national ART programme and public health leaders consider these recommendations in the context of countries' HIV epidemics, the strengths and weaknesses of health systems, and the availability of financial, human and other essential resources.(*1*) Care must be exercised to avoid undermining current treatment programmes, to protect access for the most at-risk populations, to achieve the greatest impact for the greatest number of people and to ensure sustainability.

5. FUNDING AND DECLARATIONS OF INTEREST

Funding to support this work comes from the US President's Emergency Plan for AIDS Relief (PEPFAR), The United Nations Joint Programme on HIV/AIDS Unified Budget and Workplan (UNAIDS UBW), and specific funds through staff time.

Declaration of interest forms were collected from every member of each guidelines working group. Two declarations of interest were made. Dr Charles Holmes declared previous employment, which ceased in January 2008, by Gilead Sciences, largely for phase 1 studies of experimental ARVs. This interest was assessed by the WHO Secretariat as not sufficient to preclude Dr Holmes' participation in this meeting. Dr Pedro Cahn acted as a member of the Peer Review Group and declared that he serves as advisory board member for Abbott, Bristol Myers Squibb, Tibotec, Merck, Avexa, Pfizer and Gilead. This interest was assessed by the WHO Secretariat as not sufficient to preclude Dr Cahn's participation in this meeting.

6. GUIDING PRINCIPLES

The principles guiding the development of these recommendations were as follows:

- to prioritize the best options for treatment of HIV infection and propose alternatives if the best option was not available;
- to be clear when high-quality evidence supports a strong recommendation;
- to be clear when low-quality evidence or an uncertain balance between risks and benefit supports a conditional recommendation;
- to be both realistic and aspirational, recognizing the possibility for progressive implementation of the recommendations over the lifetime of these guidelines until 2012.

7. OBJECTIVES OF THE GUIDELINES AND TARGET AUDIENCE

- To provide evidence-based recommendations outlining a public health approach to the delivery of ART for adults and adolescents, with a focus on settings with limited health systems capacity and resources.
- To identify the most potent, effective and feasible first-line, second-line and subsequent treatment regimens as components of expanded national responses for HIV care.
- To develop recommendations applicable to the majority of populations regarding the optimal timing of ART initiation, preferred first-line and second-line ARV regimens and improved criteria for ART switching, and to introduce the concept of third-line ART regimens.

The **target audiences** are national treatment advisory boards, partners implementing HIV care and treatment, and organizations providing technical and financial support to HIV care and treatment programmes in resource-limited settings.

8. METHODOLOGY AND PROCESS

Throughout 2009, WHO worked to update the guidelines for *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach* through a series of coordinated efforts to review and synthesize new and emerging evidence on the optimal use of ART within a public health approach. This process was based on the preparation GRADE profiles, systematic and targeted reviews, risk-benefit analyses, technical reports and assessments of impact, feasibility and cost.

All evidence documentation prepared for these guidelines is available on the *2009-2010 ART guidelines for adults and adolescents evidence map* web page (http://www.who.int/hiv/topics/treatment/evidence3/en/index.html).

Preparatory work included the following:

- GRADE profiles on when to start ART, what to use in first-line and second-line regimens and when to switch to second-line therapy.
- Systematic and targeted reviews on:
  - the management of HIV/hepatitis and HIV/TB coinfection;
  - ART safety, toxicity and teratogenicity;
  - the utility of CD4 count and viral load in monitoring ART;
  - ART failure criteria;
  - third-line ART;
  - interactions between ARVs and opioids, and drugs used for the treatment of tuberculosis (TB), viral hepatitis and malaria.
- Consultations with PLHIV.
- A report on ART adherence.
- A review of current ART guidelines from 26 countries.
- Costing information based on studies of procurement and production of ARVs.
- An impact assessment of the number of patients in need of treatment according to various CD4 count thresholds.
- A feasibility analysis for the introduction of the proposed guidelines in Malawi.

Search strategies employed in the systematic reviews, meta-analyses and GRADE profiles which were conducted by the Cochrane HIV/AIDS group followed methodology described in *The Cochrane handbook for systematic reviews of interventions* (Version 5.0.2; last updated September 2009, available at http://www.cochrane-handbook.org/.

In reviews where data were not amenable to meta-analysis and/or GRADE profiles, systematic searches, using relevant key words and search strings, were conducted of electronic databases (Medline/Pubmed, Embase, CENTRAL), conference databases (Aegis, AIDSearch, NLM Gateway and hand searches) and clinical trial registers (http://clinicaltrials.gov/ www.controlled-trials.com www.pactr.org).

This guideline revision is in accordance with procedures outlined by the *WHO Guidelines Review Committee* and is based on the GRADE approach to evidence review. The process involved four

separate working groups: the *Internal WHO ART Guideline Working Group,* the *ART Guideline Drafting Group*, the external *ART Peer Review Panel* and the full *ART Guideline Review Committee*. The composition of the groups was in accordance with WHO procedures for guideline development and included HIV experts, civil society representatives, programme managers, costing experts, guideline methodologists, epidemiologists, health economists, PEPFAR technical working group representatives, PLHIV community representatives, and WHO regional and country officers. Declarations of Interests were submitted by group participants.

The work was coordinated by the Antiretroviral, Treatment and HIV Care team of the WHO Department of HIV/AIDS.

The academic institutions that contributed to writing the guidelines were the Liverpool Medical School (UK), the South African Medical Research Council / South African Cochrane Centre (South Africa), the University of California, San Francisco / Cochrane Collaborative Review group on HIV/AIDS (USA), the University of New South Wales (Australia) and the University of Bern (Switzerland). Contributions were also received from the US Centers for Disease Control and Prevention (CDC), UNAIDS and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Consultations were held with civil society networks including the Global Network of People Living with HIV (GNP+), the International Treatment Preparedness Coalition (ITCP) and the International Community of Women with HIV/AIDS (ICW).

Group processes were managed as follows. The proposed recommendations were considered separately by the ART Guideline Working and Drafting Groups using a risk-benefit analysis tool consisting of a table exploring the following domains: existing and proposed recommendations, evidence for the outcomes deemed critical (mortality, disease progression and serious adverse events), risks and benefits of implementing the recommendations, acceptability, costs, feasibility, suggested ranking of recommendations (strong or conditional), gaps and research needs. The groups placed emphasis on concerns and important outcomes as voiced by PLHIV and on the critical need to maintain equity, access and coverage.

The draft recommendations, GRADE profiles, risk-benefit analysis tables and supporting data were circulated to the *ART Peer Review Panel* for comment before convening the multidisciplinary *ART Guideline Review Committee* in October 2009. Following the release of *Rapid advice* in November 2009, successive drafts of the full guidelines were prepared and circulated to the *ART Guideline Drafting Group* and the external *ART Peer Review Panel* for comments. All responses were considered and addressed in the final draft. Disagreements were resolved in discussions.

The guidelines will be disseminated as a paper-based handbook and electronically on the WHO web site.

Regional and subregional meetings are planned to adapt these global recommendations to local needs and facilitate implementation.

A plan will be developed to evaluate the implementation of the guidelines by users.

A review of the guidelines is planned for 2012. There will be interim reviews as new evidence becomes available.

9. FROM EVIDENCE TO RECOMMENDATION

Recommendations contained in the 2006 guidelines were based on levels of evidence from randomized clinical trials (RCTs), scientific studies, observational cohort data and, where insufficient evidence was available, expert opinion. Each recommendation was rated using the criteria described in Table 1, the letters A, B, and C representing the strengths of the recommendations and the numerals I, II, III and IV representing the quality of the evidence. Cost-effectiveness, acceptability and feasibility were not explicitly considered.

Table 1. Assessment of evidence as used in the 2006 guidelines

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

In the 2010 guidelines the development of a recommendation remains guided primarily by the quality of evidence using GRADE methodology. However, the GRADE approach includes the additional domains of the balance between risks and benefits, acceptability (values and preferences), cost and feasibility. Values and preferences may differ in regard to desired outcomes or there may be uncertainty about whether an intervention represents a wise use of resources. Furthermore, despite clear benefits, it may not be feasible to implement a proposed recommendation in some settings.

Table 2. Assessment of strengths of recommendations as used in the 2010 guidelines

Strength of recommendation	Rationale
Strong	The panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.

Strength of recommendation	Rationale
Conditional	The panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However: the recommendation is only applicable to a specific group, population or setting OR new evidence may result in changing the balance of risk to benefit OR the benefits may not warrant the cost or resource requirements in all settings.
No recommendation possible	Further research is required before any recommendation can be made.

In the GRADE approach, the quality of a body of evidence is defined as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The usefulness of an estimate of the effect of an intervention depends on the level of confidence in that estimate. The higher the quality of evidence, the more likely a strong recommendation can be made. It is not always possible to prepare GRADE profiles for all interventions.

Table 3. Assessment of strength of evidence as used in the 2010 guidelines

Evidence level	Rationale
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

Table 4. Additional domains considered in developing strengths of recommendations

Domain	Rationale
Benefits and risks	When developing a new recommendation, desirable effects (benefits) need to be weighed against undesirable effects (risks), considering any previous recommendation or an alternative. The larger the gap or gradient in favour of the benefits compared to the risks, the more likely a strong recommendation will be made.
Values and preferences (acceptability)	If the recommendation is likely to be widely accepted or valued more highly, a strong recommendation will probably be made. If there is a great deal of variability or if there are strong reasons that the recommended course of action is unlikely to be accepted, it is more probable that a conditional recommendation will be made.
Costs / financial implications (resource use)	Lower costs (monetary, infrastructure, equipment or human resources), or greater cost-effectiveness will more probably result in a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected to be attained, a strong recommendation is more probable. Tools have been developed to assist national ART advisory committees when assessing the feasibility of implementing a new recommendation. These are available at: http://www.who.int/hiv/topics/treatment/evidence3/en/index.html

10. ADAPTING THE GUIDELINES

WHO normative guidelines are developed for a global audience and it is expected that each country will adapt the recommendations to suit its own circumstances. WHO endorses the use of a national technical or advisory treatment working group to direct the adaptation process. It is recognized that the implementation of some recommendations may be challenging in some settings in view of the differing prevalence of HIV and of limited available and promised resources. It is recognized that the new recommendations have the potential to increase substantially the number of people eligible for ART and to increase the cost of delivering ART as part of comprehensive care. Immediate and full implementation of these recommendations may not be practicable, feasible or affordable. However, country-level strategic planning should be directed towards eventually implementing these recommendations and achieving national universal access to HIV care and treatment. It is recommended that national ART advisory committees consider the following six guiding principles to direct decision-making when introducing the revised recommendations.

1. Do no harm

Seek to maintain current progress of treatment programmes without disrupting the care of those on treatment or compromising PLHIV at highest risk for poor outcomes.

2. Accessibility

Ensure that all clinically eligible people infected with HIV are able to enter treatment services.

3. Quality of care

Ensure that care achieves the highest standards possible.

4. Equity of access

Ensure fairness and justice in access to treatment services.

5. Efficiency in resource use

Aim to achieve the greatest health impact with the optimal use of available human and financial resources.

6. Sustainability

Understand the long-term consequences of changes and have the vision to provide continued, lifelong access to ART for those in need.

While the six guiding principles should be used to direct decision-making, contextual issues must also be taken into consideration, and it is not expected that all national ART advisory committees will come to the same decisions. It is important to engage stakeholders, including PLHIV, civil society and health-care workers, in open discussions about how to make choices and implement changes.

In addition, the following points should be considered.

1. Strengthen health systems

In making decisions, priority should be given to interventions that will directly or indirectly strengthen health systems.

2. Implement in phases

It may not be possible to implement every new recommendation in every setting. A phased approach may be necessary if only some recommendations can be implemented.

3. Understand the perspectives of PLHIV

The toxicity of d4T is of concern to the majority of PLHIV and its continuing use may undermine confidence in ART. If d4T has to be included in ongoing regimens, strategies should be devised to allow for substituting an alternative drug in cases of toxicity. There should be a plan to eventually avoid the routine use of this drug.

4. Be forward-looking

The WHO guideline *Antiretroviral therapy for HIV infection in adults and adolescents* will next be updated in 2012. Member States should strive to adopt the 2010 recommendations before that date.

An adaptation guide has been written to accompany these guidelines. WHO recognizes that the new recommendations will promote significant benefits to HIV-infected individuals, and also that they have the potential to substantially increase the number of people in need of ART and the cost of delivering it. Depending on how the new guidelines are implemented or interpreted, they could also lead to unintended consequences, such as reduced access to those most in need or the undermining of existing ART coverage or impending ongoing or planned research. The purpose of the adaptation guide is to assist Member States and programme managers to choose and prioritize the recommendations, especially where resources are limited. In addition, the guide is intended to serve as an advocacy tool for policy-makers and to provide a basis for difficult choices and decisions in Member States. The adaptation guide is available at: http://www.who.int/hiv/topics/treatment/guide_for_adaptation.pdf.

To further assist countries, programme managers, academic institutions and national ART advisory committees to adapt these new recommendations to their local circumstances, the following materials are available on the WHO main evidence map web page. http://www.who.int/hiv/topics/treatment/evidence3/en/index.html.

11. SUMMARY OF CHANGES

Earlier initiation of ART

On the basis of the available evidence the panel recommended ART initiation for all PLHIV with a CD4 count of ≤350 cells/mm^3 and for those with WHO clinical stage 3 or 4 if CD4 testing is not available.

Simplified, less toxic antiretroviral drugs for use in first-line and second-line therapy

While current options have permitted rapid ART scale-up, the cost in terms of side-effects has been considerable. There is a clear demand both from PLHIV and health-care providers to phase in less toxic ARVs while maintaining simplified fixed-dose combinations. The available evidence indicates that initial ART should contain an NNRTI (either NVP or EFV) plus two NRTIs, one of which should be 3TC or FTC and the other AZT or TDF. Countries are advised to choose one second-line regimen for individuals with first-line failure.

Promoting the initiation of ART for all those with HIV/TB coinfection

While recognizing that this recommendation will be challenging for many countries with a significant HIV and TB burden, the panel placed high value on reducing the impact of TB on societies and on the data demonstrating a reduction in all-cause mortality among individuals provided with TB therapy and ART.

Promoting improved HBV diagnosis and more effective treatment of HIV/HBV coinfection

Evidence supports the initiation of ART, irrespective of WHO disease stage or CD4 cell count, for all those with HIV/HBV coinfection and chronic active hepatitis B when treatment is indicated for hepatitis B. However, there is no agreed definition of chronic active hepatitis in resource-limited settings. Despite this, the panel felt that it was necessary to include the principles of optimum care for those with HIV/HBV coinfection and bring these into alignment with recommendations in well-resourced settings. There is an urgent need to develop diagnostic criteria to identify individuals with HIV/HBV coinfection who need treatment in situations where HBV DNA and liver biopsy are not routinely available.

More strategic monitoring for antiretroviral efficacy and toxicity

While laboratory monitoring should not be a barrier to initiating ART, the newly recommended ARV regimens may require more laboratory monitoring than current regimens, especially in individuals at higher risk for adverse events. A phased-in approach to the use of viral load testing, if feasible, will improve the identification of treatment failure.

12. RECOMMENDATIONS AT A GLANCE

When to start	All adolescents and adults including pregnant women with HIV infection and CD4 counts of ≤350 cells/mm^3, should start ART, regardless of the presence or absence of clinical symptoms. Those with severe or advanced clinical disease (WHO clinical stage 3 or 4) should start ART irrespective of their CD4 cell count.
What to use in first-line therapy	First-line therapy should consist of an NNRTI + two NRTIs, one of which should be zidovudine (AZT) or tenofovir (TDF). Countries should take steps to progressively reduce the use of stavudine (d4T) in first-line regimens because of its well-recognized toxicities.
What to use in second-line therapy	Second-line ART should consist of a ritonavir-boosted protease inhibitor (PI) plus two NRTIs, one of which should be AZT or TDF, based on what was used in first-line therapy. Ritonavir-boosted atazanavir (ATV/r) or lopinavir/ritonavir (LPV/r) are the preferred PIs.
Laboratory monitoring	All patients should have access to CD4 cell–count testing to optimize pre-ART care and ART management. HIVRNA (viral-load) testing is recommended to confirm suspected treatment failure. Drug toxicity monitoring should be symptom-directed.
HIV/TB coinfection	Irrespective of CD4 cell counts, patients coinfected with HIV and TB should be started on ART as soon as possible after starting TB treatment.
HIV/HBV coinfection	Irrespective of CD4 cell counts or WHO clinical stage, patients who require treatment for HBV infection should start ART. First-line and second-line regimens for these individuals should contain TDF and either emtricitabine (FTC) or lamivudine (3TC).

Table 5. When to start antiretroviral therapy

Target population	2010 ART guideline	2006 ART guideline
HIV+ asymptomatic ARV-naive individuals	CD4 ≤350 cells/mm^3	CD4 ≤200 cells/mm^3
HIV+ symptomatic ARV-naive individuals	WHO clinical stage 2 if CD4 ≤350 cells/mm^3 **OR** WHO clinical stage 3 or 4 irrespective of CD4 cell count	WHO stage 2 or 3 and CD4 ≤200 cells/mm^3 WHO stage 3 if CD4 not available WHO stage 4 irrespective of CD4 cell count Consider treatment for WHO clinical stage 3 and CD4 cell count between 200 and 350 cells/mm^3
HIV+ pregnant women	CD4 ≤350 cells/mm^3 irrespective of clinical symptoms **OR** WHO clinical stage 3 or 4 irrespective of CD4 cell count	WHO stage 1 or 2 and CD4 ≤200 cells/mm^3 WHO stage 3 and CD4 ≤350 cells/ mm^3 WHO stage 4 irrespective of CD4 count
HIV/TB coinfection ARV-naive individuals	Presence of active TB disease, irrespective of CD4 cell count	Presence of active TB disease and CD4 ≤350 cells/mm^3 ART Initiation can be delayed if CD4 ≥200 cells/mm^3
HIV/HBV coinfection ARV-naive individuals	Individuals who require treatment for their HBV infection*, irrespective of CD4 cell count	No specific recommendation

* The current diagnosis of chronic active hepatitis in well-resourced settings is based on histological parameters obtained by liver biopsy and/or the availability of HBV DNA testing, neither of which is usually available in resource-limited settings. A global definition of chronic active hepatitis in the context of resource-limited settings based on clinical signs and simpler laboratory parameters is under discussion.

Table 6. What antiretroviral therapy to start

Target population	2010 ART guideline	2006 ART guideline
HIV+ ARV-naive adults and adolescents	No change, but in settings where d4T regimens are used as the principal option for starting ART a progressive plan to move towards AZT-based or TDF-based first-line regimens should be developed, based on an assessment of cost and feasibility	AZT or TDF + 3TC (or FTC) + EFV or NVP
HIV+ pregnant women	AZT preferred but TDF acceptable EFV included as a NNRTI option (but do not initiate EFV during first trimester) Benefits of NVP outweigh risks where CD4 count is 250–350 cells/mm^3 In HIV+ women with prior exposure to MTCT regimens, see ART recommendations in section 13.2	AZT + 3TC + NVP
HIV/TB coinfection	No change ART should be initiated as soon as possible in all HIV/TB-coinfected patients with active TB (within 8 weeks after the start of TB treatment)	AZT or TDF + 3TC (or FTC) + EFV
HIV/HBV coinfection	NNRTI regimens that contain both TDF + 3TC (or FTC) are required	TDF + 3TC (or FTC) + EFV

Table7. Recommended second-line antiretroviral therapy

Target population	2010 ART guideline*		2006 ART guideline
HIV+ adults and adolescents	If d4T or AZT used in first-line therapy	TDF + 3TC (or FTC) + ATV/r or LPV/r	ABC + ddI or TDF+ ABC or ddI +3TC or TDF + 3TC (± AZT) plus ATV/r or FPV/r or IDV/r or LPV/r or SQV/r
	If TDF used in first-line therapy	AZT + 3TC (or FTC) + ATV/r or LPV/r	

Target population	2010 ART guideline*		2006 ART guideline
HIV+ pregnant women	Same regimens as recommended for adults and adolescents		ABC + ddI or TDF+ ABC or ddI +3TC or TDF + 3TC (± AZT) plus LPV/r or NFV or SQV/r
HIV/TB coinfection	If rifabutin available (150 mg 3 times/ week)	Same regimens as recommended for adults	ABC + ddI or TDF+ ABC or ddI +3TC or TDF + 3TC (± AZT) plus LPV/r or SQV/r with adjusted dose of RTV (LPV/r 400 mg/400 mg twice a day or LPV/r 800 mg/200 mg twice a day or SQV/r 400 mg/400 mg twice a day)
	If rifabutin not available	Same NRTI backbones recommended for adults plus LPV/r or SQV/r with adjusted dose of RTV (LPV/r 400 mg/400 mg twice a day or LPV/r 800 mg/200 mg twice a day or SQV/r 400 mg/400 mg twice a day)	
HIV/HBV coinfection	AZT + TDF + 3TC (or FTC) + ATV/r or LPV/r		3TC- and/or TDF-containing regimens

* ABC and ddI can be considered as backup options in case of AZT or TDF toxicity or if AZT or TDF are contraindicated.

13. WHEN TO START

13.1. Recommendations

1. It is recommended to treat all patients with CD4 counts of ≤350 cells/mm^3 irrespective of the WHO clinical stage.
   (Strong recommendation, moderate quality of evidence)
2. It is recommended that all patients with WHO clinical stage 1 and 2 should have access to CD4 testing to decide when to initiate treatment.
   (Strong recommendation, low quality of evidence)
3. It is recommended to treat all patients with WHO clinical stage 3 and 4 irrespective of CD4 count.
   (Strong recommendation, low quality of evidence)

In making these recommendations, the *ART Guideline Review Committee* (the "panel") placed high value on avoiding death, disease progression and the likely risk of HIV transmission over and above cost and feasibility.

13.2. Evidence

The evidence used in formulating recommendations on when to start ART comes from a systematic review: *Optimal time of initiation of antiretroviral therapy for asymptomatic, HIV-infected, treatment-naive adults.*(*2*) The review included randomized controlled clinical trials (RCTs) and cohort studies, in which ART initiation was stratified according to CD4 cell count. On the basis of GRADE methodology, the evidence was rated for each of the critical and important outcomes to determine whether or not to change the current WHO guideline.

The recommendations are supported by moderate quality evidence for critical patient and public health outcomes from one unpublished RCT and one post hoc analysis nested in an RCT. In the GRADE evidence profile, pooled data from these two studies provide moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/mm^3 reduces mortality rates in asymptomatic, ART-naive, HIV-infected people. The panel also reviewed large observational data sets from both resource-limited and well-resourced settings that were consistent with data from the RCT, but these did not add to the overall quality of evidence. The panel considered the recommendations to be feasible if introduced in a phased manner, with the speed and completeness determined by health-system capacity, HIV burden, ART coverage, equity of access and funding.

Recent modelling and observational data suggest that more than 50% of HIV-infected patients with WHO clinical stage 2 may have a CD4 count of ≤350 cells/mm^3. However, considering the uncertain prognostic value of some WHO clinical stage 2 conditions, the panel recommended that HIV-infected individuals with WHO clinical stage 1 and 2 should have access to CD4 testing to decide if treatment should be initiated.

13.3. Summary of findings

Moderate-quality evidence supports strong recommendations for the timing of ART initiation for the critical outcomes of absolute risk of death, disease progression (including tuberculosis), and the occurrence of serious adverse events.

One RCT specifically aimed to determine the optimal time to initiate ART in asymptomatic, treatment-naive, HIV-infected adults. The *CIPRA HT-001 (2009) study*, a single-centre trial in Haiti, randomized 816 ART-naive participants with a CD4 count of 200–350 cells/mm^3, to receive early treatment (start ART within 2 weeks of enrolment) versus standard-of-care treatment (start ART when the CD4 count is <200 cells/mm^3 or following the development of an AIDS-defining illness).(*3*) The median CD4 count at study entry was 280 cells/mm^3 in the early treatment group and 282 cells/mm^3 in the standard-of-care group. The primary study end-point was survival and the secondary end-point was incident TB. The Data Safety and Monitoring Board (DSMB) recommended cessation of the study after a median follow up of 21 months (1–44 months). Deaths and incident TB occurred in 6 and 18 patients respectively in the early group compared to 23 and 36 patients in the delayed group (mortality HR 4.0, p = 0.0011; incident TB HR 2.0, p = 0.0125). Of the participants in the standard-of-care group, 40% reached a CD4 cell count of <200 cells/ mm^3, developed an AIDS-defining illness or died.

Early ART initiation was examined further in one subgroup post hoc analysis (249 participants) nested in a larger RCT. The *SMART* trial was a multicentre study conducted at 318 sites in 33 high-income and low/middle-income countries, which randomized 5472 participants with CD4 cell counts of >350 cells/mm^3 to either a viral suppression strategy (goal of maximal and continuous viral suppression) versus a drug conservation strategy (ART deferred until CD4 was <250 cells/mm^3).(*4*) In a subset analysis of 477 patients who were ART-naive at study entry (n = 249) or who had not received ART for >6 months before randomization (n = 228) and who were randomized to start ART immediately (with CD4 of >350 cells/mm^3) or delayed until after CD4 dropped to <250 cells/mm^3, there was a reduction of disease progression and serious non-AIDS events when ART was initiated before the CD4 cell count dropped to ≤350 cells/mm^3 compared with delaying until the CD4 count was <250 cells/mm^3.

In the GRADE profile, pooled data from this RCT and the subgroup post hoc analysis provided moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/mm^3 reduced mortality rates in asymptomatic, ART-naive HIV-infected people. Evidence regarding a reduction in morbidity was less strong because there were few events. The numbers of adverse events were also small.

As the *CIPRA-HT001 2009* trial was conducted in a resource-limited setting, the applicability of these results in determining a change in WHO guidelines is high.

The GRADE profile notes that the quality of these data was limited by imprecision (there was only one RCT), indirectness (the *SMART* data come from a post hoc subset analysis) and reporting bias (there may be other trials which did not conduct or publish similar analyses of potential subsets within the original trials).

The results from the *CIPRA HT-001* and *SMART* trials are consistent with four observational cohort studies from resource-limited and well-resourced countries, which showed that early initiation of ART was associated with reduced morbidity and mortality.(*5–8*) GRADE tables were not produced for the four observational studies identified in the systematic review as they would not have increased the overall quality of evidence. No trials were identified which evaluated the optimal timing of initiation of ART in people coinfected with hepatitis B, hepatitis C or both.

13.4. Benefits and risks

Benefits

Modelling estimates predict that the initiation of ART for individuals with a CD4 cell count of ≤350 cells/mm^3 or with WHO clinical stage 3 or 4 will result in the numbers of people on ART increasing by 49% and a reduction in HIV-related mortality of 20% by 2010–2015.(*9*) Further modelling data suggest additional transmission benefit from earlier initiation of ART for both sexual transmission and MTCT of HIV providing that there is high treatment coverage and high adherence.(*10*) Earlier initiation and more time spent on ART may provide impetus to shift to less toxic first-line regimens and reduced prices for newer fixed-dose combinations (FDCs).

Observational and RCT data confirm that there is an increased risk of TB and invasive bacterial diseases as CD4 cell counts decline.(*11,12*) Conversely, there is a 54% to 92% reduction in TB in individuals receiving ART.(*13*)

Risks

It is estimated that increasing the threshold for ART initiation can increase ART cost up to 57% by 2010–2015.(*9*) Broadening the criteria for treatment may result in some persons in urgent need of treatment being displaced by persons for whom treatment would be beneficial but not as urgent. In recommending a higher CD4 count threshold for initiation, a guiding principle is that those most in need of treatment should retain priority access.

Earlier initiation will mean longer exposure to ART (estimated to be 1 to 2 years more) and the possibility of more ART-related side-effects and ARV resistance. It remains unclear if asymptomatic individuals will accept HIV testing or ART. Additionally, the impact of earlier initiation on adherence is uncertain.

13.5. Acceptability and feasibility

In consultations with PLHIV, the benefits of starting ART earlier were recognized and strongly supported. However, concern was voiced about the increased risk of adverse events, resistance to first-line ARVs, drug stock-outs, and unavailability of second-line regimens. While earlier ART initiation will reduce the current disparity between treatment recommendations in resource-limited and well-resourced settings, it will appear to decrease treatment coverage. Ministries and donors may feel under pressure to address immediate increased costs. Feasibility will be enhanced if there is a phased introduction of the higher thresholds, with the speed and completeness determined by the health system's capacity, HIV burden, ART coverage and funding.

13.6. Clinical considerations

Table 8. WHO clinical staging of HIV disease in adults and adolescents

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (under 10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulcerations
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections
Clinical stage 3
Unexplained severe weight loss (over 10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than 1 month
Unexplained persistent fever (intermittent or constant for longer than 1 month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, meningitis, pyomyositis, bone or joint infection, bacteraemia, severe pelvic inflammatory disease)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained 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
HIV wasting syndrome
Pneumocystis jiroveci pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus disease (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis including meningitis
Disseminated nontuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including nontyphoidal *Salmonella*)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Source: Revised WHO clinical staging and immunological classification of HIV and case definition of HIV for surveillance. 2006.

Table 9. Criteria for ART Initiation in specific populations

Target population	Clinical condition	Recommendation
Asymptomatic individuals (including pregnant women)	WHO clinical stage 1	Start ART if CD4 ≤350
Symptomatic individuals (including pregnant women)	WHO clinical stage 2	Start ART if CD4 ≤350
	WHO clinical stage 3 or 4	Start ART irrespective of CD4 cell count
TB and hepatitis B coinfections	Active TB disease	Start ART irrespective of CD4 cell count
	HBV infection requiring treatment*	Start ART irrespective of CD4 cell count

* The current standard definition of chronic active hepatitis in industrialized countries is mainly based on histological parameters obtained by liver biopsy, a procedure not usually available in the large majority of resource-limited settings. A global definition of chronic active hepatitis for resource-limited settings based on clinical and more simple laboratory parameters is under discussion.

While increased access to CD4 testing is a priority, the lack of a CD4 cell count should not be a barrier to the initiation of ART. For ART programmes in many countries with the highest HIV burden, clinical criteria remain the basis for deciding when to initiate ART. In both resource-limited and well-resourced settings, there is a move towards earlier initiation of ART. However, many people still present for the first time with advanced HIV disease, with a CD4 count of <200 cells/mm^3 or with an opportunistic infection.(*14,15*)

Clinical assessment

Clinical staging is intended for use where HIV infection has been confirmed by HIV antibody testing. It is used to guide decisions on when to start cotrimoxazole prophylaxis and when to start ART. Table 8 (*WHO clinical staging of HIV disease in adults and adolescents*) and Annex 21.5 (*Diagnostic criteria for HIV-related clinical events in adults and adolescents*) provide details of specific staging conditions and the criteria for recognizing them.

For individuals with advanced HIV disease (WHO clinical stage 3 or 4), ART should be initiated irrespective of the CD4 cell count. Both stages 3 and 4 are independently predictive of HIV-related mortality.(*16–19*) Assessing the need for ART in those with WHO clinical stage 2 presents challenges. Some stage 2 conditions may be considered more indicative of HIV disease progression than others. For example, papular pruritic eruptions (PPEs) typically occur with CD4 counts of <200 cells/mm^3, and most physicians would recommend the initiation of ART in the presence of PPEs and the absence of a CD4 count.(*20,21*) Conversely, recurrent oral ulceration or a fungal nail infection generally would not be considered triggers to start ART. Given the uncertainty with which stage 2 conditions predict mortality and disease progression, HIV-

infected individuals with WHO clinical stage 2 should have priority access to CD4 testing to decide if treatment should be initiated. The same recommendation to promote CD4 testing applies to asymptomatic individuals (WHO stage 1). The objective is to identify those with a low CD4 count, are still well, but need to start ART.

Immunological assessment

Expanded provider-initiated testing and counselling (PITC) and voluntary counselling and testing (VCT), together with immunological assessment (CD4 testing), are critical to achieving the goals of earlier diagnosis and starting ART before people become unwell or present with their first opportunistic infection.(*22*) A CD4 cell count performed at entry into care or prior to ART initiation will guide the decision on when to start ART and serves as the baseline if CD4 testing is used for ART monitoring. ART should be commenced in individuals with a CD4 count of ≤350 cells/mm^3. Absolute CD4 cell counts fluctuate within individuals and with intercurrent illnesses. If feasible, CD4 testing should be repeated if a major management decision rests on the value, rather than using a single value. Serial CD4 measurements are more informative than individual values because they reflect trends over time. The total lymphocyte count (TLC) is no longer recommended to guide treatment decisions in adults and adolescents.

Virological assessment

In resource-limited settings, plasma viral load (HIVRNA) measurement is not required before the initiation of ART. However, expanded access to viral load testing is needed to improve the accuracy of diagnosing treatment failure. Earlier detection of virological failure allows both targeted adherence interventions and better preservation of the efficacy of second-line regimens.(*23*)

14. WHAT TO START

14.1. Recommendations

Start one of the following regimens in ART-naive individuals eligible for treatment.

- AZT + 3TC + EFV
- AZT + 3TC + NVP
- TDF + 3TC (or FTC) + EFV
- TDF + 3TC (or FTC) + NVP

(Strong recommendation, moderate quality of evidence)

Because stavudine (d4T) is relatively inexpensive and is currently a component of first-line therapy in many countries, the panel specifically considered studies of d4T-based regimens. In making these recommendations, the panel placed high value on avoiding the disfiguring, unpleasant and potentially life-threatening toxicity of d4T, in addition to the selection of regimens suitable for use in most patient groups, treatment durability and the benefits of using fixed-dose combinations. The available information suggests that abacavir (ABC) and didanosine (ddI) have serious constraints for use in first-line regimens (toxicities and cost) and the panel focused on comparisons between AZT, TDF and d4T-based regimens.

14.2. Evidence

Using Cochrane systematic review methodology, triple-drug ARVs for the initial treatment of HIV infection were examined in RCTS, other controlled trials, and cohort and case-control studies. The comparisons of interest were mortality, disease progression, virological response to ART (the proportion of individuals who suppressed viral replication to undetectable levels, defined as <40, <400 or <500 copies/ml), serious adverse events (*Division of AIDS adverse event toxicity scale*, National Institute of Allergy and Infectious Diseases, USA, 2004), adherence, tolerability and retention, and immunological response to ART (median or mean change in CD4 cell count from baseline). The quality of evidence was assessed using GRADE evidence profiles.

The following specific interventions were compared:

- dual NRTI backbone with d4T versus dual NRTI backbone with AZT;
- dual NRTI backbone with TDF versus dual NRTI backbone with AZT or d4T;
- 2 NRTIs + NVP versus 2 NRTIs + EFV.

Current evidence suggests that the new recommended regimens are comparable in terms of efficacy, with a better overall toxicity profile than d4T-based regimens. The panel was reassured by the GRADE evidence profile from RCTs, non-randomized trials and observational studies from low-income and middle-income countries, which indicate no superiority for the outcomes of interest of AZT over TDF, or of NVP over EFV as part of combination ART for treatment-naive individuals.

14.3. Summary of main findings

This systematic review did not find any evidence from RCTs, non-randomized trials or observational studies from resource-limited settings that clearly indicated the superiority of regimens based on AZT, d4T or TDF or the superiority of either EFV or NVP, in triple-drug antiretroviral regimens for treatment-naive patients.

Studies which compared or are comparing AZT and d4T in different combinations provide reasonably robust evidence that AZT-containing and d4T-containing regimens are equivalent. (*24–33*) These studies have a variety of limitations and the overall GRADE evidence profile rating was very low. Five of the six studies were open-label, several studies compared AZT + 3TC to d4T + ddI, potentially obscuring the head-to-head comparison of AZT and d4T, and others used protease inhibitors as a third drug. The A*dult Antiretroviral Treatment and Resistance Study* (TSHEPO study) in Botswana is directly comparing combinations of AZT + 3TC + NVP or EFV and d4T + 3TC + NVP or EFV.(*34*)

Three RCTs have compared regimens containing TDF to d4T or AZT. Two of these studies used 3TC as the second NRTI and allowed for direct comparisons (*35,36*); the third compared AZT + 3TC with TDF + FTC.(*37*) Two of these studies had equivalent findings; that efficacy and safety were similar for AZT + 3TC + EFV and d4T + 3TC + EFV, and for TDF + FTC + EFV and TDF + 3TC + EFV. (*35,36*)

The third study compared TDF + 3TC to AZT +3TC, both with once-daily NVP, and was prematurely discontinued after failure of the TDF + 3TC + NVP arm to suppress viral replication in 8 of 35 participants(*35,36*). In two other small studies, similar rates of failure to suppress viral replication have also been found in patients receiving NVP once daily.(*38,39*) However, in the large ARTEN study, (atazanavir/ritonavir on a background of tenofovir and emtricitabine vs. nevirapine) in which 569 patients were randomized to receive NVP 200 mg BID, NVP 400 mg OD or ATV /r 300/100mg OD each given with TDF/FTC OD, non-inferiority of the primary end-point (undetectable VL at week 48) was established between the combined NVP arms and ATV/r arm. (*40*)

Data from *AIDS therapy evaluation in the Netherlands (*ATHENA) and *Swiss HIV cohort study* (4471 on NVP twice-daily and 629 on NVP once-daily regimens) suggest that NVP once daily is at least as efficient as NVP prescribed twice daily.(*41*)

Additional evidence comes from observational studies which were not included in the GRADE profile. None were conducted in low-income and middle-income settings. These studies showed that TDF-containing backbones were associated with a higher proportion of non-detectable viraemia,(*42*) a lower rate change due to toxicity,(*43*) overall greater durability (*44*) and slower rates of CD4-cell increase.(*45,46*) Two observational studies reported that TDF/FTC or 3TC was cost-saving compared to AZT+3TC.(*47,48*)

Six RCTs which have compared NVP to EFV found no differences in efficacy.(*49–54*) One RCT reported that EFV was less likely than NVP to be associated with the development of antiretroviral resistance.(*53*) The GRADE evidence profile is moderate to high, with the exception of drug

resistance, which was examined in only a single study. Ongoing studies will add substantially to this literature.(*55–57*)

The systematic review of d4T safety and toxicity prepared for this guideline revision reported data from three RCTs and 24 observational studies, demonstrating the consistent association between d4T and peripheral neuropathy, lipoatrophy and lactic acidosis.

14.4. Benefits and risks

Benefits

Phasing in AZT and TDF will reduce the risk of acute d4T-related lactic acidosis and of long-term mitochondrial toxicities (particularly lipoatrophy and peripheral neuropathy), and has the potential for improved adherence and reduced lost to follow-up. TDF can be included in a once-daily FDC. The combination of TDF + 3TC or FTC is the recommended NRTI backbone in the presence of HBV coinfection. AZT + 3TC is a preferred NRTI backbone option in pregnant woman. There will be fewer within-class changes with more durable and safer regimens.

Risks

AZT and TDF may require more laboratory monitoring than d4T-based regimens. There may be concern from PLHIV and care providers about anaemia (AZT) and renal toxicity (TDF). There is uncertainty whether TDF requires renal screening and monitoring in all individuals or only in selected populations (elderly, those with low body weight, those taking concomitant renal toxic drugs or with diseases such as diabetes and hypertension). TDF has been reported as associated with bone mineral loss.(*58*) Recently, safety and effectiveness in adolescents was reviewed; individuals aged ≥12 years and weighing ≥35 kg should use the dose recommended in adults.(*58*) In addition to anaemia, AZT is associated with initial gastrointestinal adverse events, proximal myopathy and skin hyperpigmentation. Not all of these options are currently available as a full FDC (AZT + 3TC + EFV; TDF + 3TC + NVP; TDF + FTC + NVP).

While progressive reduction in the use of d4T is occurring, it may be retained as an interim measure if plans are initiated to monitor and manage toxicity. In certain situations, d4T may be retained as a backup drug, such as when TDF and AZT are contraindicated.

14.5. Acceptability and feasibility

As current evidence suggests that the recommended regimens are comparable in terms of efficacy, countries should select one of them as the preferred option for most patients initiating ART, on the basis of factors related to acceptability and feasibility, such as:

- numbers of individuals needing to start ART according to 2010 and 2015 targets;
- numbers of individuals starting ART who have HIV/TB coinfection or chronic active HIV/HBV coinfection;
- anaemia (due to malaria, malnutrition, intestinal parasites, repeated pregnancies or other causes);
- pregnant women or women of reproductive age;

- predicted expenditure per person needing ART (based on selected national start criteria);
- availability of FDC;
- in-country cost of the drug regimens;
- decisions by countries on laboratory requirements to monitor toxicities;
- training needs for the introduction and management of the regimens;
- countries may need to use modelling to assist in decision-making.

Table 10. Preferred first-line ART in treatment-naive adults and adolescents

Target population	Preferred options	Comments
Adults and adolescents	AZT or TDF + 3TC or FTC + EFV or NVP	Select the preferred regimens applicable to the majority of PLHIV Use fixed-dose combinations
Pregnant women	AZT + 3TC + EFV or NVP	Do not initiate EFV during first trimester TDF acceptable option In HIV women with prior exposure to PMTCT regimens, see ART recommendations in Table 11
HIV/TB coinfection	AZT or TDF + 3TC or FTC + EFV	Initiate ART as soon as possible (within the first 8 weeks) after starting TB treatment NVP or triple NRTIs are acceptable options if EFV cannot be used
HIV/HBV coinfection	TDF + 3TC or FTC + EFV or NVP	Consider HBsAg screening before starting ART, especially when TDF is not the preferred first-line NRTI Use of two ARVs with anti-HBV activity required

14.6. The choice between NVP and EFV

NVP and EFV have comparable clinical efficacy when administered in combination regimens. However, differences in toxicity profiles, the potential for interaction with other treatments, and cost should be considered when an NNRTI is being chosen.(*54,59*)

NVP is associated with a higher incidence of rash, Stevens-Johnson syndrome, and hepatotoxicity compared to EFV.(*54*) The simultaneous initiation of NVP and other new drugs that can also cause rash (e.g. cotrimoxazole) should be avoided where possible. In the case of severe hepatic or skin reactions, NVP should be permanently discontinued and not restarted. NVP is the

preferred NNRTI for women if there is potential for pregnancy or during the first trimester of pregnancy. While there are conflicting data regarding an increased risk of hepatic toxicity in women with CD4 counts between 250 and 350 cells/mm^3, the panel found that there was limited evidence to cause concern but still urged caution in the use of NVP in women with CD4 counts of >250 cells/mm^3 or in those with unknown CD4 cell counts. Close clinical monitoring (and laboratory monitoring if feasible) during the first 12 weeks of therapy is recommended when NVP is initiated in women with a CD4 cell count of 250–350 cells/mm^3.

EFV can be used once daily, is generally well tolerated but is more costly and currently less widely available than NVP. Its primary toxicities are related to the central nervous system (CNS) and possible, but not proven teratogenicity, if received during the first trimester of pregnancy (but not in the second and third trimesters), and rash. Rash is generally mild and self-resolving and usually does not require the discontinuation of therapy. The CNS symptoms are common. While they typically resolve after 2–4 weeks, they can persist for months, resulting in discontinuation of the drug. 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. EFV is the NNRTI of choice in individuals with TB/HIV coinfection who are receiving rifampicin-based TB therapy.

There are clinical situations when individuals need to replace EFV with NVP. The most common scenarios are when patients temporarily change from NVP to EFV because they need to take rifampicin-containing TB treatment and subsequently switch back to NVP on completion of TB treatment, and individuals with persistent EFV CNS intolerance. In this case, EFV can be stopped and full-dose NVP (200 mg twice daily) can be started immediately. There is no need for lead-in NVP dosing.(*60,61*)

14.7. AZT + 3TC + EFV option

In recommending this as a preferred first-line regimen, the panel placed high value on the utility of EFV in the treatment of HIV/TB coinfection.

Efficacy and safety

Low (for AZT) to moderate (for EFV) GRADE evidence profiles for the critical outcomes of mortality, clinical progression and serious adverse events support this option.

In the systematic review of AZT toxicity, low body mass and low CD4 cell count were independent predicators of developing AZT-induced anaemia.*(62,63)* Background rates of anaemia vary considerably. Malaria, pregnancy, malnutrition and advanced HIV disease are well-recognized risk factors for anaemia. The prevalence, incidence and predictors of severe anaemia with AZT-containing regimens in African adults were assessed in the *Development of antiretroviral therapy in Africa* (DART) trial.(*63*) More than 6% of individuals receiving AZT developed grade 4 (ACTG toxicity grading scale) anaemia by 12 months. In data from nine PEPFAR focus countries, 12% stopped AZT because of anaemia or gastrointestinal intolerance.(*64*) In Uganda, 25% of 1029 patients who initiated a d4T-containing ART were switched to AZT because of d4T toxicity,(*65*) and 5% subsequently switched to another drug because of AZT toxicity.

The EFV toxicity review showed consistent reports of self-limiting or tolerable CNS adverse events and uncertainties about teratogenic risk in humans. In the important outcome (as distinct from the predetermined critical outcomes of mortality, disease progression and adverse events) of ARV resistance, EFV may be superior to NVP.(*66*)

EFV should not be initiated in the first trimester of pregnancy but may be initiated in the second and third trimesters. There is conflicting evidence of very low quality on the risks of EFV causing neural tube defects. The overall rates of birth defects reported in association with EFV, NVP, LPV/r or TDF appear similar and are consistent with rates reported in congenital defects registries from general populations. However, neural tube birth defects are rare, with an incidence 0.1% in the general population. Prospective data are currently insufficient to provide an assessment of neural tube defect risk with first-trimester exposure, except to rule out a potential tenfold or higher increase in risk (i.e. an increase in risk from 0.1% to >1%). Since neural tube closure occurs by approximately 28 days of gestation and very few pregnancies are recognized by this time, the potential risk with the use of EFV in women who might conceive while receiving the drug is difficult to estimate. Women who are planning to become pregnant or who may become pregnant should use a regimen that does not include EFV, in order to avoid the highest risk period of exposure *in utero* (conception to day 28 of gestation). If a woman is diagnosed as pregnant before 28 days of gestation, EFV should be stopped and substituted with NVP or a PI. If a woman is diagnosed as pregnant after 28 days of gestation, EFV should be continued. There is no indication for termination of pregnancy in women exposed to EFV in the first trimester of pregnancy.

Risk, benefits and acceptability

AZT requires twice daily dosing and currently there is no AZT-containing triple-drug FDC (a dual FDC containing AZT + 3TC is available).

Potentially troublesome AZT toxicities, such as proximal myopathy, gastrointestinal intolerance, skin hyperpigmentation and lipodystrophy, are not uncommon.

EFV is preferred in individuals taking rifampicin-containing TB treatment. EFV is not approved in children under 3 years of age (and there are insufficient data on appropriate dosing for that age group). Recent single-dose NVP for the prevention of mother-to-child transmission (PMTCT) may compromise response to EFV because of cross-resistance. EFV is associated with CNS adverse events, which are common.

14.8. AZT + 3TC + NVP option

In recommending this as a preferred first-line regimen, the panel placed high value on it as the preferred option in pregnancy. It is widely available, there is extensive experience in its use and the cost is lower than an EFV-containing regimen.

Efficacy and safety

NVP may be inferior to EFV in the important, noncritical outcome of ARV resistance (as distinct from the predetermined critical outcomes of mortality, disease progression and serious adverse events).(*53*) Based on safety concerns raised in some of these studies, the US FDA has cautioned

against the use of NVP in women with high CD4 cell counts. This current review of NVP safety in women with CD4 counts of 250–350 cells/mm^3 did not confirm an increased risk of serious adverse events. Available evidence is based largely on retrospective reviews or open-label studies, with one RCT and two post hoc analyses within an RCT (2NN study) informing the evidence profile. (*54,67*) The data are conflicting, with increased rates of hepatotoxicity and hypersensitivity reported in some studies (*54,67–72*) and not in others.(*73–80*) Two of these trials were in pregnant women. Other studies reported no difference in adverse events between those with low and high CD4 cell counts in virologically suppressed patients switching to NVP.(*76,81,82*) These studies support the concept that a suppressed viral load is a protective factor for NVP-related hypersensitivity in the situation where patients need to switch from an EFV-based (or PI-based) regimen to NVP. While there is a good representation of studies in resource-limited settings, the key recommendation regarding cautious use of NVP in the presence of higher CD4 cell counts is from high-income and middle-income settings.(*54*) An increased risk of hypersensitivity and hepatoxicity has been reported in men with a CD4 count of >400 cells/mm^3.(*83*)

The panel found that there was limited evidence to cause concern about the use of NVP in women with CD4 counts of 250–350 cells/mm^3 but urged caution in the use of NVP in women with CD4 counts of >250 cells/mm^3 or in those with unknown CD4 cell counts. The panel concluded that the benefits of using NVP in this situation outweigh the risks of not initiating ART but still urged close clinical monitoring (and laboratory monitoring if feasible) during the first 12 weeks of therapy when NVP is initiated in women with a CD4 cell count of 250–350 cells/mm^3 or with an unknown CD4 cell count and in men with a CD4 cell count of >400 cells/mm^3 or with an unknown CD4 cell count.

Risk, benefits and acceptability

The regimen is widely available, applicable to paediatric and adult populations and a preferred option in pregnancy, and there is large programmatic experience. Triple FDC formulations are available for adults and children. Some countries have moved to or are considering this combination already. PLHIV want low pill-burden and FDC options, but AZT and NVP adverse events may be unacceptable. NVP-associated hepatotoxicity /skin rash can be life-threatening (but there is an unclear relationship with CD4 and gender). Rifampicin and NVP drug-drug interactions are such that the combination should not be used unless no alternative is available. The NVP lead-in dose adds complexity. Recent single-dose NVP (sdNVP) use for PMTCT may compromise virological response.(*84*)

14.9. TDF + 3TC (or FTC) + EFV option

In recommending this as a preferred regimen, the panel placed high value on the simplicity of use (potential for one pill once daily) and the treatment of HIV/HBV coinfection.

Efficacy and safety

The GRADE evidence profiles summarize evidence of low (for TDF) and moderate (for EFV) quality supporting the use of TDF + 3TC (or FTC) + EFV for the critical outcomes of mortality, clinical progression and serious adverse events. Existing TDF toxicity data suggest low rates of

renal toxicity in prescreened patients. However, baseline rates of renal disease in African patients seem to be higher than in non-African populations.

The GRADE evidence profile produced for this guideline revision demonstrated no difference in the occurrence of adverse events (changes in creatinine, proteinuria, all grade 3 or 4 adverse events or treatment discontinuation) in patients using TDF-containing regimens compared to other regimens. Imprecision (one pharmacokinetic study) and study limitations (small sample size) were reported in the profile. The cumulative incidence of nephrotoxicity in TDF-containing regimens has been reported as 1% to 4%, and the rate of Fanconi's syndrome as 0.5% to 2.0%, with no association between renal disease and gender, age or race.(*85,86*) Only one study (open-label, 86 participants) reported data from resource-limited settings (Argentina, Brazil, Dominican Republic), with no discontinuations attributable to renal adverse events.(*87*) A 2007 report of all postmarketing adverse drug reactions up to April 2005 for 10 343 patients in developed countries using TDF reported observations of renal serious adverse events in 0.5% of individuals and graded elevations of serum creatinine in 2.2%. Risk factors for increased serum creatinine were concomitant nephrotoxic medications, elevated serum creatinine, low body weight, advanced age and lower CD4 cell count. One study of 15 pregnant women with limited treatment options reported creatinine clearance of >90 ml/min in all but one, who had a transient decline.(*88*)

Risk, benefits and acceptability

A triple FDC is available with low pill-burden (one pill once daily) which is well accepted by PLHIV.

Two drugs in the regimen are active against HBV, no lead-in dosing is required, and the combination can be used in patients receiving rifampicin-containing TB treatment. There are limited data on the use of TDF without renal screening or monitoring in resource-limited settings. TDF is not approved in children and adolescents and there are limited data on the safety of TDF in pregnancy.

Clinicians may have concerns about TDF use without renal monitoring, especially in individuals at higher risk for renal complications. There will be additional cost if laboratory monitoring of creatinine is required. The regimen may only be feasible where renal screening is available or not a prerequisite.

An alternative non-EFV-containing regimen is required in the context of the first trimester of pregnancy or for women seeking to become pregnant.

14.10. TDF + 3TC (or FTC) + NVP option

In recommending this as a preferred first-line regimen, the panel placed high value on lower cost compared to EFV-containing regimens and the treatment of HIV/HBV coinfection.

Efficacy and safety

TDF and NVP are discussed in previous sections.

Risk, benefits and acceptability

Two drugs in the regimen are active against HBV. There is a relatively low pill burden and the potential for a once-daily regimen. There is limited programmatic experience with this combination and there have been reports of higher rates of virological failure when compared to TDF + 3TC or FTC + EFV.(*53*)

14.11. Triple NRTI option

It is recommended that the triple nucleoside regimens AZT + 3TC + ABC or AZT + 3TC + TDF should be used for individuals who are unable to tolerate or have contraindications to NNRTI-based regimens, particularly in the following situations:

- HIV/TB coinfection;
- pregnant women;
- chronic viral hepatitis B;
- HIV-2 infection.

(Conditional recommendation, low quality of evidence)

These two triple NRTI regimens may be considered as alternative first-line treatments in situations such as intolerance to both NNRTIs, or where an NVP-containing regimen is contraindicated and EFV is not available, in coinfection with TB or chronic hepatitis B, or in HIV-2 infection. Recent data from the DART trial, where the large majority of patients are taking AZT + 3TC + TDF, showed good clinical response and survival rates of around 90% over 5 years of follow-up.(*63*) However, some specific triple NRTI combinations, such as ABC + 3TC + TDF and TDF + ddI + 3TC, showed high rates of virological failure and should not be used. In HIV-2 infection, some studies suggest a higher risk of virological failure with the triple nucleoside regimen of AZT + 3TC + ABC when compared with boosted PI regimens.

14.12. Stavudine (d4T)

In resource-limited settings, d4T continues to play a critical role in the scaling up of ART, where approximately 56% of HIV regimens still contain d4T.(*89*) Alternative options (AZT and TDF) are more expensive, require more laboratory monitoring and have higher initial discontinuation rates.(*35,90*) Cumulative exposure to d4T has the potential to cause disfiguring, painful and life-threatening side-effects, such as lipodystrophy, peripheral neuropathy and lactic acidosis. (*91,92*)

Studies have identified several risk factors associated with d4T-related adverse events. Peripheral neuropathy was significantly associated with older age (over 35 or 40 years).(*93–95*) Lipodystrophy and hyperlactataemia were significantly associated with BMI >25 and female gender.(*93,96,97*) Female gender and high baseline weight were also significantly related to symptomatic hyperlactataemia/lactic acidosis and lipodystrophy in South Africa.(*98*)

On the issue of progressive reduction in the use of d4T in settings where d4T regimens are used as the principal option for starting ART, countries should develop a plan to move towards AZT-based or TDF-based first-line regimens, on the basis of an assessment of cost and feasibility. Systems to prevent, monitor and manage d4T-related toxicities should be implemented. Safer but currently more expensive first-line ARTs should be progressively introduced as currently they may not be feasible or affordable in many high-burden settings with low coverage, less developed health systems, limited laboratory capacity, finite budgets and competing health priorities. In countries with high coverage and more developed health systems, transition to new treatment regimens should occur sooner. If d4T use is continued, it should be dosed at 30 mg BID for all individuals, irrespective of body weight.(*99*)

14.13. NRTIs not to be used together

Certain dual NRTI backbone combinations should not be used in 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 and should be avoided.

15.1. Recommendations for HIV-infected pregnant women

1. Start ART in all pregnant women with HIV and a CD4 count of ≤350 cells/mm^3, irrespective of clinical symptoms.
   (Strong recommendation, moderate quality of evidence)
2. CD4 testing is required to determine if pregnant women with HIV and WHO clinical stage 1 or 2 disease need to start ARV treatment or ARV prophylaxis for PMTCT.
   (Strong recommendation, low quality of evidence)
3. Start ART in all pregnant women with HIV and WHO clinical stage 3 or 4, irrespective of CD4 count.
   (Strong recommendation, low quality of evidence)
4. Start one the following regimens in ART-naive pregnant women eligible for treatment:

- AZT + 3TC + EFV;
- AZT + 3TC + NVP;
- TDF + 3TC (or FTC) + EFV;
- TDF + 3TC (or FTC) + NVP.

(Strong recommendation, moderate quality of evidence)

5. Do not initiate EFV during the first trimester of pregnancy.
   (Strong recommendation, low quality of evidence)

In making these recommendations, the ART and PMTCT panels placed high value on ensuring that treatment begins early for pregnant women with HIV, improving maternal and child-health outcomes and avoiding MTCT, over and above concerns about cost or feasibility.

When to start

On the question of when to start, no studies specific to pregnant women were identified in the systematic review prepared for this guideline revision. Evidence from the general population supports strong recommendations for the timing of initiation in terms of reduction of mortality, disease progression, serious adverse events, the risk of TB and the risk of HIV transmission (sexual and mother to child). As with the recommendation on when to start in the general population, the panel recognized the uncertainty around the prognostic value of some WHO clinical stage 2 conditions, and data from modelling and observational studies indicating that more than 50% of HIV-infected patients with WHO clinical stage 2 have a CD4 count of ≤350 cells/mm^3. The panel therefore recommended that all pregnant women with WHO clinical stages 1 and 2 should have access to CD4 testing in order to decide when to start treatment.

What to start

On the question of what to start, no GRADE evidence profiles were prepared as no RCTs were identified that compared the use of different ARV regimens in pregnant women. Cohort studies report a reduction of HIV transmission and death.(*100*) There is no evidence to suggest an increase in maternal serious adverse events and there are no studies specifically evaluating

maternal response to ART. Registry data on the use of TDF in pregnancy show no signals to raise concern, and there is no evidence to suggest that TDF + 3TC (or FTC) is not an acceptable alternative to AZT + 3TC.(*101,102*)

As discussed in the section on EFV, there is very low quality conflicting evidence on the risks of EFV causing neural tube defects, with the overall rates of birth defects reported in association with EFV, NVP and TDF similar to rates reported in congenital defects registries of general populations. However, data are currently insufficient to determine whether there is an increased risk of rare anomalies such as neural tube defects with first-trimester EFV exposure.

The review of NVP safety in pregnant women with CD4 counts between 250 and 350 cells/mm^3 did not confirm an increased risk of serious adverse events. However, while data from two prospective cohorts indicate no association between NVP and liver enzyme elevation, pregnancy itself was associated with an increased risk of any liver enzyme elevation and that this association was present, regardless of prior ART and NVP exposure history.(*103*) The panel concluded that the benefits of using NVP in pregnancy outweighed the risks. The panel was unable to conclude from the evidence reviewed whether there were benefits associated with the use of EFV compared to NVP in pregnant women after the first trimester and with higher or unknown CD4 cell counts, although more than half of the panel members preferred EFV in these situations.

15.2. Recommendations for women with prior exposure to antiretrovirals for PMTCT

1. Initiate a non-NNRTI-based ART in women who have received single-dose nevirapine (sdNVP) alone or in combination with other drugs without an NRTI tail within 12 months of initiating chronic ART. If an NNRTI-based regimen is started, perform viral load testing at 6 months and, if there are >5000 copies/ml, switch to a bPI-based regimen.
2. Initiate a standard NNRTI-based ART regimen in women who have received sdNVP alone or in combination with other drugs with an NRTI tail within 12 months of initiating chronic ART and perform viral load-testing at 6 months. If the viral load is >5000 copies/ml, changing to a bPI is recommended.
3. Initiate a standard NNRTI-based ART regimen in women who have received sdNVP (alone or in combination with other drugs) more than 12 months before starting therapy (with or without a NRTI tail) if possible. The viral load should be evaluated at 6 months and if it is >5000 copies/ml a change in the bPI-based regimen is required.

Initiate a standard NNRTI regimen in women who have received ARV drugs such as AZT alone, without sdNVP, for PMTCT.

Table 11. ART regimens recommended for women with prior exposure to PMTCT regimen

Previous ARV exposure for PMTCT	Recommendations for initiation of ART when needed for treatment of HIV for maternal health
sdNVP[1] (+/- antepartum AZT) with no AZT/3TC tail[2] in last 12 months	Initiate a non-NNRTI regimen PI preferred over 3 NRTI
sdNVP (+/- antepartum AZT) with an AZT/3TC tail in last 12 months	Initiate an NNRTI regimen If possible, check viral load[3] at 6 months and if >5000 copies/ml, switch to second-line ART with PI
sdNVP (+/- antepartum AZT) with or without an AZT/3TC tail over 12 months ago	Initiate an NNRTI regimen If possible, check viral load[3] at 6 months and if >5000 copies/ml, switch to second-line ART with PI
Option A[4] Antepartum AZT (from as early as 14 weeks of gestation) sdNVP at onset of labour* AZT + 3TC during labour and delivery* AZT + 3TC tail for 7 days postpartum* * sd-NVP and AZT + 3TC can be omitted if mother receives >4 weeks of AZT antepartum	Initiate an NNRTI regimen If possible, check viral load[3] at 6 months and if >5000 copies/ml, switch to second-line ART with PI If no sdNVP was given, start standard NNRTI (viral load does not need to be checked unless clinically indicated as no sdNVP received)
All triple ARV regimens (including **Option B**), irrespective of duration of exposure and time since exposure **Option B**[4] Triple ARV from 14 weeks gestation until after all exposure to breast milk has ended AZT + 3TC + LPV/r AZT + 3TC + ABC AZT + 3TC + EFV TDF + [3TC or FTC] + EFV	Initiate standard NNRTI regimen If EFV-based triple ARV was used for prophylaxis and no tail (AZT + 3TC; or TDF + 3TC; or TDF + FTC) was given when triple ARV was discontinued after cessation of breastfeeding (or delivery if formula feeding), check viral load[3] at 6 months and if >5000 copies/ml, switch to second-line ART with PI

[1]Single-dose nevirapine (sdNVP) is one 200-mg tablet of NVP.

[2]A tail is the provision of two NRTIs, typically AZT/3TC, for a minimum of 7 days following sdNVP or the cessation of any NNRTI-based regimen with the objective of minimizing NNRTI resistance.

[3]If VL is not available, continue NNRTI regimen and monitor clinically (and immunologically if available).

[4]Options A or B are viewed as equally effective for PMTCT in women who do not require therapy for their own health and are recommended options in the 2010 update of *Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants*.

Evidence

The long half-life of NVP and its low genetic barrier to resistance means that detectable drug levels persist for 2–3 weeks in the presence of active viral replication following a single maternal dose. (*104–106*) EFV also has a long half-life, with detectable drug levels for more than 21 days following discontinuation.(*107*) This has clinical relevance in pregnancy when ARVs are provided solely for prophylaxis against perinatal transmission and discontinued after delivery or after breastfeeding. In a meta-analysis of 10 studies, the prevalence of NVP resistance 4 to 8 weeks following sdNVP was 35.7% and the prevalence of NVP resistance in infants who became infected despite prophylaxis was 52.6%.(*108*) In most women, resistant virus can no longer be detected 6 to 12 months after exposure. However, low levels of viral resistance can persist for longer periods and in some cases can remain present in latently infected cells.(*109–111*)

Data suggest that women starting NNRTI-based therapy within 6–24 months of sdNVP exposure have higher rates of viral failure than those without sdNVP exposure. A definite relationship between time from sdNVP exposure to starting NNRTI-based therapy has been observed but varied between studies from 6 months to 24 months, with a definite improvement in response if >12 months since sdNVP exposure and start of therapy.(*112–119*) A tail regimen for a minimum of 7 days is recommended following sdNVP or if NNRTI-based triple therapy ART is used for the prevention of perinatal transmission and subsequently stopped. NNRTI resistance rates of 0% to 7% at 2 to 6 weeks postpartum have been reported with the use of various tail regimens. (*120–125*)

15.3. Recommendations for HIV/HBV coinfection

1. Start ART in all HIV/HBV-coinfected individuals who require treatment for their HBV infection, (chronic active hepatitis), irrespective of the CD4 cell count or the WHO clinical stage.
   (Strong recommendation, low quality of evidence)
2. Start TDF and 3TC (or FTC)-containing antiretroviral regimens in all HIV/HBV coinfected individuals needing treatment.
   (Strong recommendation, moderate quality of evidence)

In developing these recommendations, the panel placed high value on promoting HBV diagnosis and more effective treatment of HIV/HBV coinfection. The systematic review of this topic did not find RCTs which addressed critical HIV outcomes (death, disease progression, serious adverse events) and the GRADE profile reported only on outcomes related to HBV (HBV viral load and HBV drug resistance).

Liver biopsy and HBVDNA are not usually available in the large majority of resource-limited settings. A global definition of chronic active hepatitis for resource-limited settings based on clinical and available laboratory parameters is under discussion.

When to start

On the question of when to start ART in HIV/HBV coinfection, there are no RCTs comparing early versus late initiation of ART. However, observational data demonstrate that individuals with HIV/HBV coinfection have a threefold to sixfold increased risk of developing chronic HBV infection, an increased risk of fibrosis and cirrhosis and a 17-fold increased risk of death compared to HBV-infected individuals without HIV infection.(*126,127*) Similarly, observational data support a reduction in liver-related disease with earlier and HBV-active combination ART.(*128*)

What to start

On the question of what ART to start in HIV/HBV coinfection, there are data from one RCT supporting the use of at least two agents with activity against HBV (TDF plus 3TC or FTC) in terms of improved HBV viral load response and reduced development of HBV drug resistance. (*129,130*)

15.4. Recommendations for HIV/tuberculosis coinfection

1. Start ART in all HIV-infected individuals with active TB, irrespective of the CD4 cell count. *(Strong recommendation, low quality of evidence)*
2. Start TB treatment first, followed by ART as soon as possible afterwards (and within the first eight weeks).
   (Strong recommendation, moderate quality of evidence)
3. Use efavirenz (EFV) as the preferred NNRTI in patients starting ART while on TB treatment. *(Strong recommendation, high quality of evidence)*

In making these recommendations, the panel placed high value on the reduction of early mortality from HIV/TB coinfection, the potential for reduction of TB transmission when all individuals with HIV are started on ART earlier, and improved morbidity/mortality, reduction of TB recurrence and improved management of TB for coinfected HIV/TB patients.

When to start

On the question of when to initiate ART in TB infection, one RCT (SAPIT study) provides moderate evidence for the early initiation of ART in terms of reduced all-cause mortality and improved TB outcomes.(*131*) Trial participants were grouped into “integrated” (immediate and end of TB drug initiation phases combined) and “sequential” treatment arms. Mortality was 55% lower in the integrated treatment arm (5.1/100 person-years) compared to the sequential treatment arm (11.6 per 100 person-years), which was terminated. The trial is continuing to examine the outcomes of starting ART immediately or starting at the completion of the initiation phase of TB treatment. Until further data are available, it is recommended that ART be initiated as soon as TB therapy is tolerated. Ideally, this may be as early as 2 weeks and not later than 8 weeks.

There are limited data on the initiation of ART in patients with TB and CD4 counts of >350 cells/mm^3.

Impact on TB transmission and incidence

ART has been reported to reduce TB rates by up to 90% at the individual level and by approximately 60% at the population level, and to reduce TB recurrence rates by 50%.(*13,132,133*) Modelling suggests that the initiation of ART for all those with HIV/TB coinfection, if accompanied by high levels of coverage and ART adherence, reduces the number of TB cases, TB mortality rates and TB transmission at the population level.(*134*)

What to start

The recommendations from the 2006 ART guidelines are maintained. Specifically, EFV is recommended because of less interaction with rifampicin compared to NVP. For those HIV/TB coinfected individuals who are unable to tolerate EFV, an NVP-based regimen or a triple NNRTI (AZT + 3TC + ABC or AZT + 3TC + TDF) are alternative options. In the presence of rifampicin, no lead-in dose of NVP is required.(*50,135–138*). Similarly, if patients temporarily change from NVP to EFV because they need to take rifampicin-containing TB therapy and subsequently switch back to NVP on completion of TB treatment, no lead-in dosing of NVP is required.(*60,61*)

15.5. Rifabutin

Background

Drug interactions between rifampicin and boosted protease inhibitors (bPIs) prohibit the concomitant use of standard therapies for both HIV and TB. Rifampicin induces the cytochrome P450 enzyme system, lowering standard-dose bPI plasma concentrations by 75–90%. All bPIs (at standard doses) are contraindicated with rifampicin. LPV/r or SQV/r may be used with an adjusted, superboosted dose of RTV (LPV/r 400 mg/400 mg BID or SQV/r 400 mg/400 mg BID) or doubling the standard LPV/r daily dose (LPV/r 800 mg/200 mg BID) but this is associated with high levels of toxicity, and requires close clinical and laboratory monitoring. The recommendation to use LPV/r 800 mg/200 mg BID is based on low-quality evidence and is associated with a similar level of toxicity to LPV/r 400 mg/400 mg BID. However, this option may be more feasible in RLS, as LPV/r is widely available but RTV as a sole formulation is not.(*139–142*)

There is no comparable recommendation for ATV/r, a WHO-preferred bPI (*143*). Unlike rifampicin, rifabutin has minimal effect on bPI plasma concentrations.

Evidence

In a systematic review conducted for this guideline update, ten clinical trials (five RCTs and five cohort studies) were identified, which assessed the efficacy and safety of rifabutin in TB infection with or without HIV infection. The five RCTs were included in a Cochrane review, which found no differences in TB cure or relapse rates between rifampicin and rifabutin.(*28*)

In the five cohort studies, 313 individuals received rifabutin and ART, of whom 125 received a PI. Due to methodological issues, no rigorous efficacy assessment from these studies was possible, but there was no sign of rifabutin inferiority in comparison with rifampicin.

Taken together, these studies report comparable safety and efficacy of rifabutin and rifampicin. However, evidence from RCTs comes largely from HIV-uninfected individuals, and data on the use of rifabutin with ART are limited to first-generation, usually unboosted, PIs. A further limitation is that the evidence in HIV-infected individuals receiving a bPI and rifabutin is based on only 125 patients. In addition, the clinical experience with rifabutin for TB disease in resource-limited settings is limited, especially in the context of the bPIs currently recommended by WHO.

Clinical considerations

Dosing

The recommended dose of rifabutin in the presence of a bPI is 150 mg three times per week. (*144*) However, it should be noted that this dose has been reported to result in inadequate rifabutin levels and acquired rifabutin resistance.(*145*) Rifabutin is contraindicated if administered with the new NNRTI etravirine plus a bPI (37% reduction of etravirine levels).

Adverse events

The most common adverse events associated with rifabutin are neutropenia, leucopenia, elevations of hepatic enzymes, rash and upper gastrointestinal complaints, and, more rarely, uveitis. In the systematic review, discontinuation attributable to adverse events was uncommon. This review revealed one case report of uveitis in combination with a bPI.(*146*)

Monitoring and programmatic implications

This systematic review indicates that a bPI and rifabutin coadministration will not require intensive monitoring and can be used in primary care settings. However, the DOTS strategy promotes daily administration of TB therapy, preferably in FDCs.(*147*) Intermittent dosing of rifabutin will complicate the programmatic roll-out of TB therapy and precludes the development of rifabutin-containing FDCs. Further research is needed into the pharmacokinetics of rifabutin 75 mg once-daily in the presence of bPIs. Meanwhile, the ability to use standard bPI doses outweighs the inconvenience of intermittent dosing.

16. WHEN TO SWITCH ART

16.1. Recommendations

1. Where available, use viral load (VL) to confirm treatment failure.
   (Strong recommendation, low quality of evidence)
2. Where routinely available, use VL every 6 months to detect viral replication.
   (Conditional recommendation, low quality of evidence)
3. A persistent VL of >5000 copies/ml confirms treatment failure.
   (Conditional recommendation, low quality of evidence)
4. When VL is not available, use immunological criteria to confirm clinical failure.
   (Strong recommendation, moderate quality of evidence)

In making these recommendations, the panel was concerned by the limitations of clinical and immunological monitoring for diagnosing treatment failure, and placed high value on avoiding premature or unnecessary switching to expensive second-line ART. The panel also valued the need to optimize the use of virological monitoring and ensure adherence.

16.2. Evidence

A systematic review was conducted to assess different strategies for determining when to switch antiretroviral therapy regimens for first-line treatment failure among PLHIV in low-resource settings. Standard Cochrane systematic review methodology was employed. Outcomes of interest in order of priority were mortality, morbidity, viral load response, CD4 response and the development of antiretroviral resistance.

16.3. Summary of findings

Based on the pooled analysis of the side-effects from two randomized trials (*Home-based AIDS care* [HBAC] and *Development of antiretroviral therapy in Africa* [DART]), clinical monitoring alone (compared to combined immunological and clinical monitoring or to combined virological, immunological and clinical monitoring) resulted in increases in mortality, disease progression and unnecessary switches, but there were no differences in serious adverse events.(*148,149*) However, in the HBAC trial, combined immunological and clinical monitoring was compared to combined virological, immunological and clinical monitoring, and there were no differences in mortality, disease progression, unnecessary switches or virological treatment failures.(*148*)

Viral load measurement is considered a more sensitive indicator of treatment failure compared to clinical or immunological indicators. VL may be used in a targeted or routine strategy. The objective of the targeted strategy is to confirm suspected clinical or immunological failure, maximizing the clinical benefits of first-line therapy and reducing unnecessary switching to second-line therapy. Targeted VL may also be used earlier in the course of ART (within 4 to 6 months of ART initiation) to assess adherence and introduce an adherence intervention in at-risk patients before viral mutations start to accumulate.(*150*)

The objective of the routine VL strategy is to detect virological failure early, leading to adherence interventions or changes in therapy that will limit ongoing viral replications, reduce the risk of accumulation of resistance mutations and protect the drug susceptibility of second-line and subsequent therapies.

While staying on a failing first-line therapy is associated with an increased mortality risk,(*151*) it is uncertain if VL monitoring, compared to clinical or immunological monitoring, affects critical outcomes. Immunological criteria appear to be more appropriate for ruling out than for ruling in virological failure.(*152*) Mathematical modelling that compared these three ART monitoring strategies did not find significantly different outcomes.(*153*) The use of virological monitoring strategies has been associated with earlier and more frequent switching to second-line regimens than the use of clinical/immunological monitoring strategies. However, data from ART programmes and global procurement systems also suggests that treatment switching has occurred at lower than expected rates in resource-limited settings. Low access to second-line drugs, difficulties in defining treatment failure and the limited availability of virological monitoring have been identified as important reasons for late switching. There is evidence to support a VL threshold of 5000–10 000 copies/ml to define failure in an adherent patient with no other reasons for an elevated VL (e.g. drug-drug interactions, poor absorption, intercurrent illness): this range of values is associated with higher rates of clinical progression and immunological deterioration in some cohort studies.(*154,155*)

Immunological failure is not a good predictor of virological failure. Depending on the study, 8% to 40% of individuals who present with evidence of immunological failure have virological suppression and risk being unnecessarily switched to second-line ART.(*156*)

While no consensus on ART monitoring and the diagnosis of failure was reached, the panel supported moves to reduce reliance on clinical failure definitions, expand the use immunological criteria and use viral load testing for confirmation of clinical/immunological failure in deciding when to switch to second-line therapy.

16.4. Benefits and risks

Benefits

More accurate assessment of treatment failure will reduce the delay in switching to second-line drugs. Targeted use of VL can limit unnecessary switching and routine use of VL can reduce the risk of resistance. While expensive, VL has the potential to save the cost of expensive second-line drugs by confirming that they are needed.

Risks

The optimum threshold for defining VL failure in a public health approach is still unknown, and there are limited data on the diagnostic accuracy of VL in resource-limited settings. There is a risk that resources used to expand laboratory capacity or conduct VL testing would divert funds away from expanding access to treatment.

Acceptability and feasibility

ART switching has occurred at lower than expected rates in resource-limited settings, and the limited use of virological monitoring has been identified as an important factor. Many countries are considering employing VL to optimize the use of expensive second-line drugs. The same rationale applies when third-line drugs are available. Physicians and PLHIV consider clinical and immunological monitoring insufficient to promote a timely switch and want VL monitoring. The initial and ongoing cost is high. The use of VL to confirm clinical-immunological switch (targeted approach) will cost less than the routine use of VL monitoring. Quality assurance programmes should be implemented at VL facilities irrespective of the VL strategy adopted. Central VL facilities with adequate specimen transportation from clinic to laboratory are feasible, as is point-of-care VL capacity in urban settings. Point-of-care VL capacity in rural settings is likely to remain unfeasible with current technologies. Feasibility was not systematically assessed, but targeted use of VL seemed more feasible to the panel than routine use.

16.5. Clinical considerations

One of the critical decisions in ART management is when to switch from one regimen to another for treatment failure. The 2006 recommendations on *Antiretroviral therapy for HIV infection in adults and adolescents* recognized that definitions for treatment failure were not standardized and outlined a set of definitions for ART failure based on available evidence at that time. These remain basically unchanged except that the VL threshold for failure has changed from 10 000 copies/ml in 2006 recommendations to 5000 copies/ml in the current guidelines. An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed.

Table 12. ART switching criteria

Failure	Definition	Comments
Clinical failure	New or recurrent WHO stage 4 condition	Condition must be differentiated from immune reconstitution inflammatory syndrome (IRIS) Certain WHO clinical stage 3 conditions (e.g. pulmonary TB, severe bacterial infections), may be an indication of treatment failure

Failure	Definition	Comments
Immunological failure	Fall of CD4 count to baseline (or below) OR 50% fall from on-treatment peak value OR Persistent CD4 levels below 100 cells/mm^3	Without concomitant infection to cause transient CD4 cell decrease
Virological failure	Plasma viral load above 5000 copies/ml	The optimal viral load threshold for defining virological failure has not been determined. Values of >5 000 copies/ml are associated with clinical progression and a decline in the CD4 cell count

Fig. 1. Targeted viral load strategy for failure and switching

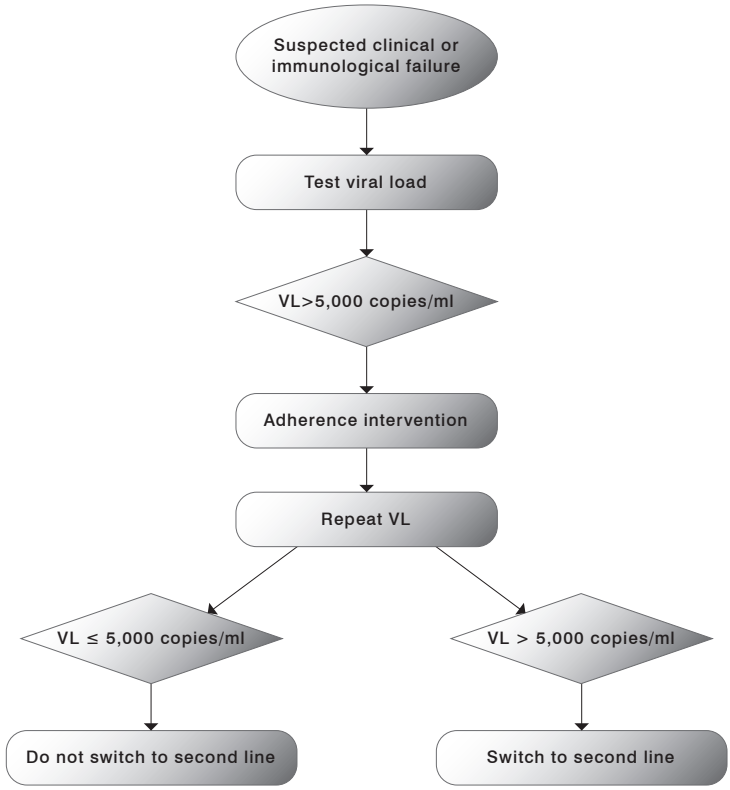
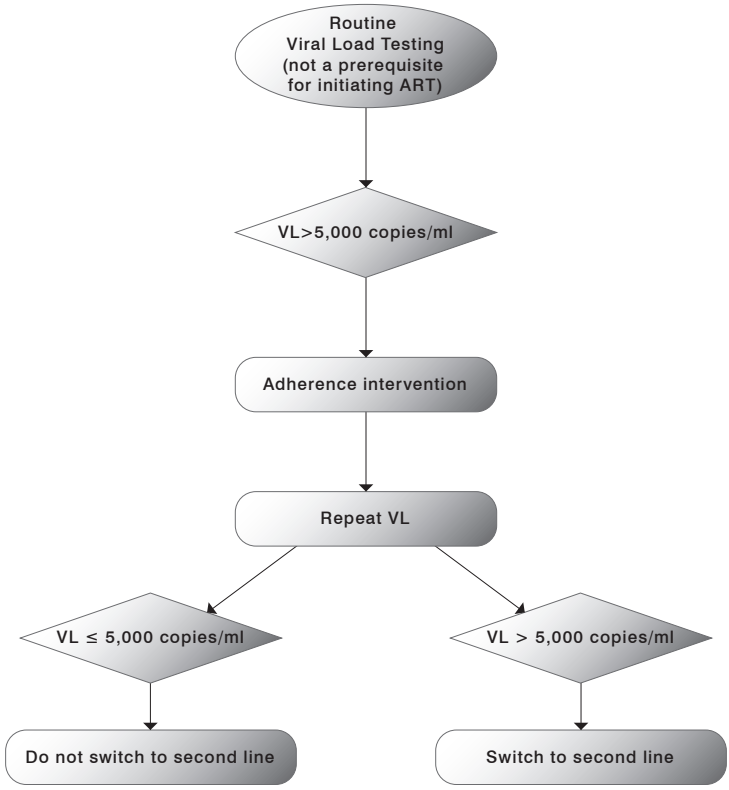


Fig. 2. Routine viral load strategy for failure and switching



NOTE: This algorithm also applies to the recommendation to check viral load 6 months after initiation of ART in women who have been exposed to sd-NVP for PMTCT.

17. SECOND-LINE REGIMENS

17.1. Recommendations

1. A boosted protease inhibitor (bPI) plus two nucleoside analogues (NRTIs) are recommended for second-line ART.
   (Strong recommendation, moderate quality of evidence)
2. ATV/r and LPV/r are the preferred bPIs for second-line ART.
   (Strong recommendation, moderate quality of evidence)
3. Simplification of second NRTI options is recommended.

- If d4T or AZT has been used in first-line therapy, use TDF + (3TC or FTC) as the NRTI backbone in second- line therapy.
- If TDF has been used in first-line therapy, use AZT + 3TC as the NRTI backbone in second- line theapy.

(Strong recommendation, moderate quality of evidence)

In making these recommendations, the panel placed high value on using simpler second-line regimens and the availability of heat-stable formulations and fixed-dose combinations.

17.2. Evidence

A systematic review was conducted with the objective of assessing the optimum second-line ART regimen in PLHIV failing first-line therapy in resource-limited settings. Standard Cochrane systematic review methodology was employed. Outcomes of interest in order of priority were mortality, morbidity (combined disease progression and serious adverse events), viral load response, CD4 response and development of antiretroviral resistance.

17.3. Summary of findings

Second-line NRTIs

Despite a comprehensive search, few studies of relevance were identified. One study reported no difference in virological outcomes among those maintaining 3TC in second-line regimens compared to those who did not (low quality of evidence).(*157*) Observational data supported this finding.(*158*)

Boosted PI comparisons

bPIs provide most of the antiviral activity in second-line regimens. There is insufficient evidence on critical patient outcomes to distinguish between bPIs in the context of second-line therapy. Randomized trials comparing LPV/r with DRV/r, ATV/r or FPV/r in ART-naive patients showed non-inferiority at 48 weeks of all three bPIs (evidence of low to moderate quality).(*159–163*) DRV/r was superior to LPV/r at 96 weeks.(*161*) There is evidence of moderate quality that ATV/r is non-inferior to LPV/r (in combination with TDF and an optimized second NRTI) in treatment-experienced patients.(*164*) Non-serious adverse events varied by boosted PI and there were no significant differences in serious adverse events.(*165,166*). All unboosted PIs are considered inferior to bPIs.

PI monotherapy

On the question of whether PI monotherapy could be used as second-line ART, there is a moderate quality of evidence from a targeted review (as opposed to a formal systematic review) of nine RCTs and individual study reports showing less virological suppression and higher rates of viral rebound for PI monotherapy compared to standard triple ART regimens.(*167–173*) There were no other significant differences in the critical outcomes of mortality, disease progression or serious adverse events, or the important outcomes of immunological response and drug resistance (both very low to moderate quality evidence). Non-critical outcomes, such as non-serious adverse events and lipoatrophy, were not captured in the GRADE evidence profile. The panel concluded that an NRTI backbone should be maintained in a second-line bPI-containing regimen.

17.4. Benefits and risks

Benefits

These recommendations will facilitate the simplification of therapeutic options and drug procurement as the NRTIs recommended in second-line therapy are also used in first-line therapy (in different combinations), and should be purchased by all programmes. There is a potential for simplified drug regimens.

Risks

There may be confusion because AZT, TDF and 3TC, the only NRTIs recommended in second-line regimens, also are recommended in first-line regimens. Some countries have already chosen alternative bPIs (IDV/r, SQV/r, FPV/r) in preference to the recommended ones (ATV/r, LPV/r).

17.5. Acceptability and feasibility

PLHIV want better second-line options with fewer side-effects. The preferred bPIs are available in most countries. Generic heat-stable LPV/r is on the market already. A generic heat-stable FDC of ATV/r (co-blister packed with TDF/3TC) is in development. Alternative bPIs (SQV, IDV, FPV and DRV) are not available as FDCs and are more expensive than the preferred options. Saquinavir has a high pill-burden, IDV has a high risk of toxicity and FPV is expensive. Clinicians may not be comfortable with not replacing both first-line NRTIs with two new NRTIs in the second-line regimen.

17.6 Clinical considerations

Table 13. Preferred second-line ART options

Target population		Preferred options	Comments
Adults and adolescents (including pregnant women)	**If d4T or AZT used in first-line therapy**	TDF + 3TC or FTC + ATV/r or LPVr	NRTI sequencing based on availability of FDCs and potential for retained antiviral activity, considering early and late switch scenarios ATV/r and LPVr are comparable and available as heat-stable FDCs or co-package formulations
	If TDF used in first-line therapy	AZT + 3TC + ATV/r or LPVr	
TB/HIV coinfection	**If rifabutin available**	Same regimens as recommended above for adults and adolescents	No difference in efficacy between rifabutin and rifampicin Rifabutin has significantly less drug interaction with bPIs, permitting standard bPI dosing
	If rifabutin not available	Same NRTI backbones as recommended for adults and adolescents plus LPVr or SQV/r with superboosted dosing of RTV (LPV/r 400 mg/400 mg twice daily or LPV/r 800 mg/200 mg twice daily or SQV/r 400 mg/400 mg twice daily)	Rifampicin significantly reduces the levels of bPIs, limiting the effective options. Use of extra doses of ritonavir with selected bPIs (LPV and SQV) can overcome this effect but with increased rates of toxicity
Hepatitis B coinfection		AZT + TDF + 3TC or FTC + ATV/r or LPVr	In case of ART failure, TDF + 3TC or FTC should be maintained for anti-HBV activity and the second-line regimen should include other drugs with anti-HIV activity

17.7. Selection of second-line NRTIs

The rationale for the selection of the NRTIs in second-line therapy is to choose the most logical combination depending on what was used in the first-line regimen. Residual activity of first-line NRTIs (with the possible exception of 3TC and FTC) is more likely the earlier failure is detected and switching is implemented. Conversely, any new NRTIs may be compromised in the second-line regimen if there is late detection of failure and late switching. The recommended NRTI sequencing is based on likely resistance mutations and the potential for retained antiviral activity.

There are two clinical scenarios:

- early switching based on sensitive monitoring for failure, using viral load;
- late switching based on insensitive monitoring, using clinical or immunological criteria for defining failure.

If AZT + 3TC are used in the first-line regimen with sensitive monitoring and early switching, the NRTIs with most likely activity are TDF and ddI. In the scenario of insensitive monitoring and late switching, TDF and ddI activity are less likely.

If TDF + 3TC are use in first-line therapy, with early or late switching, the NRTIs with remaining activity are AZT and d4T (both very likely). Retained activity of 3TC is likely in the early switching scenario and less likely in the case of late switching.(*174*)

ABC and ddI are no longer recommended as preffered options in second-line regimens. The panel concluded that there was no specific advantage in using ABC or ddI and their use added complexity and cost, but new data will be generated from ongoing trials.(*175*) One study in the review reported no difference in viral suppression following mainly d4T-based first-line ART, with and without a ddI-containing NRTI backbone in an LPV/r-based second-line regimen.(*176*) Another study reported similar virological outcomes in individuals with and without the M184V mutation and taking a second-line regimen with or without ddI.(*158*) No studies reporting failure following a first-line ABC-containing (or TDF-containing) regimen were identified.

17.8. Maintaining 3TC in the second-line regimen

There is uncertainty about whether 3TC should be added as a fourth drug in the NRTI component of second-line regimens if ddI or ABC are used as the backbone NRTIs. Only one RCT has been conducted to examine this issue; it found no significant difference in the reduction of HIVRNA in individuals who maintained 3TC in their second-line regimen compared to those who did not. (*157*) One observational study reported similar virological response among individuals with the M184V mutation (indicating resistance to 3TC and FTC) who subsequently took 3TC- or FTC-containing regimen compared to those who took a 3TC- or FTC-sparing regimen.(*177*)

17.9. NRTIs for HIV/HBV coinfection

In individuals with HIV/HBV coinfection who require treatment for their HBV infection and in whom TDF + (3TC or FTC) fail in the first-line regimen, these NRTIs should be continued in the second-line regimen for anti-HBV activity and to reduce the risk of hepatic flares, irrespective of the selected second-line regimen, which should be AZT + TDF + (3TC or FTC) + bPI.

17.10. Selection of boosted protease inhibitor

The recommend bPIs are equivalent in terms of efficacy. In studies of populations with PI resistance, there is growing support for the use of once-daily bPI regimens in which the ritonavir component is only 100 mg per day. Such regimens have fewer gastrointestinal side-effects and less metabolic toxicity than regimens that use ritonavir boosting at a dose of 200 mg per day. (*178,179*) Large head-to-head trials have demonstrated non-inferiority or superiority of ATV/r compared with LPV/r, with less gastrointestinal and lipid toxicity.(*159*)

18. THIRD-LINE REGIMENS

18.1. Recommendations

1. National programmes should develop policies for third-line therapy that consider funding, sustainability and the provision of equitable access to ART.
   (Conditional recommendation, low quality of evidence)
2. Third-line regimens should include new drugs likely to have anti-HIV activity, such as integrase inhibitors and second-generation NNRTIs and PIs.
   (Conditional recommendation, low quality of evidence)
3. Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.
   (Conditional recommendation, very low quality of evidence)

The panel was concerned by unpublished cohort reports of high mortality among patients failing second-line therapy, but placed high value on balancing the need to develop policies for third-line therapy while expanding access to first-line therapy. It was recognized that many countries have financial constraints that might limit the adoption of third-line regimens.

18.2. Evidence

A targeted literature review of relevant studies provides limited evidence to guide third-line strategies in resource-limited settings, with few studies of newer agents in these settings. Data from RCTs, predominantly in developed countries, are available for boosted darunavir (DRV/r), etravirine and raltegravir. Taken together, these data support the efficacy of these agents in highly ART-experienced patients. There was no uncertainty among the panel concerning the need for third-line regimens. However, there was uncertainty about how making third-line regimens available would affect the provision of first-line and second-line ART. There was also uncertainty about what third-line drugs should be provided, as many studies are still in progress.

18.3. Summary of findings

The evidence is very limited, particularly in resource-limited settings. However, as access to monitoring improves and the scale-up of initial ART continues, demand for second-line and third-line regimens will increase. The criteria for diagnosing second-line failure are the same as those used for diagnosing first-line failure.

In a pooled subgroup analysis, DRV/r plus an optimized background regimen (OBR) chosen by genotyping and phenotyping was shown to be superior to the control group (bPI plus OBR, where the bPI was selected by the investigator) in highly treatment-experienced individuals. (*180,181*) These studies were conducted in high- middle income countries (Argentina, Brazil) and some well-resourced settings. In a further analysis, DRV/r was well tolerated in treatment-experienced, HBV- or HCV-coinfected patients, with no differences in liver-related adverse events between DRV/r and the control bPI group.(*182*) In developed country settings, DRV/r has been reported to be cost-effective compared to LPV/r.(*183*) In individuals with limited treatment

options, raltegravir (RAL) plus OBR provided better viral suppression than OBR alone for at least 48 weeks.(*184,185*) Similarly, etravirine (ETV) plus OBR provided better viral suppression and improved immunological response than OBR alone.(*186*) In patients with multidrug-resistant virus who have few remaining treatment options, the combination of RAL, ETV, and DRV/r was well tolerated, and was associated with a rate of virological suppression similar to that expected in treatment-naive patients.(*187*)

18.4. Benefits and risks

Benefits

Therapy with newer agents is associated with a reduction in clinical progression and immunological deterioration. DRV/r has a higher genetic barrier to resistance compared to early-generation PIs and is active against multidrug-resistant HIV isolates. While high-level resistance to ETV following NVP or EFV failure appears uncommon, low-level resistance is common. (*188–190*)

Risks

There are few studies of newer agents in third-line regimens in resource-limited settings.(*191*) Most studies have been conducted in well-resourced or high-income to middle-income countries, and have demonstrated benefit for non-critical outcomes (viral load suppression or immunological improvement). There is evidence from postmarketing reports of higher rates of hypersensitivity to ETV than previously reported.(*192*) Etravirine and raltegravir are not approved for use in individuals less than 16 years of age. There are limited data on the use of newer drugs in pregnancy, including very limited pharmacokinetic and safety data.

18.5. Acceptability and feasibility

Physicians and PLHIV want a third-line regimen to be available. In studies conducted in well-resourced settings and in modelled cost-effectiveness analysis, DRV/r has been demonstrated to be cost-effective compared to other bPIs in heavily pretreated patients. The acquisition cost for ETV is one to two times higher than that of EFV and NVP. The acquisition cost of DRV and RAL has not been established in resource-limited settings but is expected to be high. The availability of these drugs in resource-limited settings now and in the near future is uncertain.

18.6. Clinical considerations

Table 14. Toxicities of third-line ARVs

Toxicities of third-line ARVs	
Darunavir (DRV)	Skin rash (10%) – DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported Hepatotoxicity Diarrhoea, nausea Headache Hyperlipidaemia Transaminase elevation Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in patients with haemophilia
Ritonavir (RTV) **(as pharmacokinetic booster)**	GI intolerance, nausea, vomiting, diarrhoea Paresthesias — circumoral and extremities Hyperlipidaemia (especially hypertriglyceridaemia) Hepatitis Asthenia Taste perversion Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in patients with haemophilia
Raltegravir (RAL)	Nausea Headache Diarrhoea Pyrexia CPK elevation
Etravirine (ETV)	Rash (2 % discontinuation because of rash during clinical trials) Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure Nausea

19. PACKAGE OF CARE INTERVENTIONS

19.1. Guiding principles

1. Countries should establish a package of care interventions, in addition to ART, to reduce HIV transmission, prevent illness and improve the quality of life.
2. A key component of the package of care interventions is the promotion of early HIV diagnosis and early assessment of ART eligibility by CD4 testing, in order to minimize late initiation of ART and maximize HIV prevention.
3. WHO continues to advocate for wider access to monitoring tools, including CD4 and viral load testing.
4. The package of care interventions should be aligned with the WHO *Essential prevention and care interventions for adults and adolescents living with HIV in resource-limited settings*.(*193*)

Not all PLHIV are eligible for ART. However, it is imperative that as many PLHIV as possible enter care before they become ill with their first opportunistic infection (OI) or before they develop advanced immunosuppression (CD4 cell count <200 cells/mm^3), which puts them at higher risk of developing opportunistic disease. Expanded access to HIV testing and counselling, especially provider-initiated but also client-initiated, is critical to identifying people who need to enter care. The pre-ART period in care provides a setting for interventions to prevent further transmission of HIV, to treat and prevent other illnesses, to prepare for the time when ART will be necessary and to maximize long-term retention in care.

19.2. Voluntary counselling and testing and provider-initiated testing and counselling

Client-initiated voluntary counselling and testing (VCT) is the process whereby the client requests a test. However, attendance at any health facility offers an opportunity to integrate discussion of HIV and HIV testing into routine medical care through provider-initiated testing and counselling (PITC).(*22*) PITC facilitates early HIV diagnosis, partner diagnosis and enrolment into pre-ART care, and minimizes late initiation of ART.

19.3. Preventing further transmission of HIV

From a public health perspective, PLHIV make up the most important group to address with HIV prevention strategies.(*194*) A change in the risk behaviour of a person with HIV has a greater impact on the transmission of HIV than the same behavioural change in a person without HIV. (*195*) Enrolment into care facilitates the identification of PLHIV with behavioural risk factors and interventions to reduce risk, and facilitates the identification of clinical risk factors, such as sexually transmitted infections and treatment, and interventions to reduce unplanned pregnancies and mother-to-child transmission of HIV.(*196*)

Pre-ART care includes harm reduction for people who inject drugs (supportive environment, opioid substitution therapy and the provision of clean needles and syringes). This not only reduces HIV transmission but has the potential to stabilize the persons' lifestyles by limiting active drug use in preparation for ART initiation.

Positive prevention strategies, at group and individual levels, have demonstrated a reduction in HIV risk behaviours among people with HIV. They include support to improve the consistency of condom use, a reduction of needle-sharing and unprotected sex among people who inject drugs, and a reduction in the number of sexual partners.(*197–199*)

19.4. The Three I's for HIV/TB

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. Pre-ART care provides a setting for implementation of the WHO *Three I's* strategy: isoniazid preventive treatment (IPT) where indicated, intensified case finding (ICF) for active TB, and TB infection control (IC) at all clinical encounters, which are key public health strategies to decrease the impact of TB among individuals and the community. The *Three I's* should be a central part of HIV care and treatment and are critical for the continued success of ART scale-up.(*200*) TB infection control is essential to keep vulnerable patients, health-care workers and their communities safe from becoming infected with TB.(*200*) Information about TB should be provided to all people with HIV. Counselling should include information about the risk of acquiring TB, strategies for reducing exposure, clinical manifestations of TB disease, and the risk of transmitting TB to others.

19.5. Cotrimoxazole prophylaxis

Cotrimoxazole prophylaxis is recommended for all symptomatic individuals (WHO clinical stages 2, 3 or 4) including pregnant women. Where CD4 testing is available, cotrimoxazole prophylaxis is recommended for individuals with a CD4 cell count of <350 cells/mm^3, particularly in resource-limited settings where bacterial infection and malaria are prevalent among PLHIV. If the main targets for cotrimoxazole prophylaxis are *Pneumocystis jiroveci* pneumonia and toxoplasmosis infection, a CD4 threshold of <200 cells/mm^3 may be chosen. Data from an observational analysis in the DART trial showed that the use of cotrimoxazole prophylaxis reduced mortality by 50% in severely immune-suppressed HIV-infected adults initiating ART, with benefits continuing for at least 72 weeks. Furthermore, cotrimoxazole prophylaxis reduced malaria incidence in these patients.(*201*)

19.6. Sexually transmitted infections

Pre-ART (and on-ART) care is an opportunity to provide comprehensive STI services, which should include correct diagnosis by syndrome or laboratory test, provision of effective treatment at the first encounter, notification and treatment of partners, reduction of further risk behaviour and transmission through education, counselling and the provision of condoms. Laboratory

screening should include a serological test for syphilis, especially in pregnant women, and HIV testing for all individuals diagnosed with an STI.(*196*)

19.7. Treatment preparedness

There is evidence that some PLHIV do not have access to accurate knowledge about HIV, the effectiveness of ART and the challenges of adherence.(*202*) In resource-limited settings, major factors contributing to good adherence are free ARVS, ease of use, and preparedness for use. (*203*) Modelling studies suggest that treatment readiness is associated with improved adherence once ART has commenced.(*204*) Enrolment into care before the time of initiation of ART provides an opportunity for PLHIV to learn, understand and prepare for successful lifelong ART.

19.8. Early initiation of ART

Enrolment into pre-ART care is critical for the early initiation of ART, maximizing treatment response and minimizing treatment complication such as immune reconstitution inflammatory syndrome (IRIS).(*205,206*) In reality, most people do not receive any pre-ART care, presenting with advanced HIV disease, and this results in delayed initiation of ART. Mortality rates during the first year of ART are high (3–26%), most deaths occurring in the first few months, largely because of late presentation.(*207*) The fundamental need is for earlier HIV diagnosis, enrolment into care, ideally with CD4 count monitoring to determine eligibility for ART, and the initiation of ART before sickness occurs.(*208*)

19.9. ART as prevention

Studies continue to support the benefits of ART for prevention.(*209*) There is evidence that individuals on fully suppressive ART who are adherent to the therapy are less likely to transmit HIV to sexual partners. Conversely, those with unrecognized HIV infection contribute significantly to onward sexual transmission. At an individual level, ART reduces viral load and infectiousness. (*210*) The use of ARV drugs has been proved to reduce MTCT of HIV.

20. LABORATORY MONITORING

20.1. Guiding principles

1. Laboratory monitoring is not a prerequisite for the initiation of ART.
2. CD4 and viral load testing are not essential for monitoring patients on ART.
3. Symptom-directed laboratory monitoring for safety and toxicity is recommended for those on ART.
4. If resources permit, use viral load in a targeted approach to confirm suspected treatment failure based on immunological and/or clinical criteria.
5. If resources permit, use viral load in a routine approach, measured every 6 months, with the objective of detecting failure earlier than would be the case if immunological and/or clinical criteria were used to define failure.

Table 15. Laboratory monitoring before, during and after initiating ART

Phase of HIV management	Recommended test	Desirable test
At HIV diagnosis	CD4	HBsAg
Pre-ART	CD4	
At start of ART	CD4	Hb for AZT[1] Creatinine clearance for TDF[2] ALT for NVP[3]
On ART	CD4	Hb for AZT[1] Creatinine clearance for TDF[2] ALT for NVP[3]
At clinical failure	CD4	Viral load
At immunological failure	Viral load	
Women exposed to PMCT interventions with sd-NVP with a tail within 12 months and without a tail within 6 months of initiating ART	Viral load 6 months after initiation of ART	

[1] Recommended test in patients with high risk of adverse events associated with AZT (low CD4 or low BMI).

[2] Recommended test in patients with high risk of adverse events associated with TDF (underlying renal disease, older age group, low BMI, diabetes, hypertension and concomitant use of a boosted PI or nephrotoxic drugs).

[3] Recommended test in patients with high risk of adverse events associated with NVP (ART-naive HIV+ women with CD4 of >250 cells/mm^3, HCV coinfection).

Patients who are not yet eligible for ART should have CD4 count measurement every six months and more frequently as they approach the threshold to initiate ART. If feasible, HBsAg should be performed in order to identify people with HIV/HBV coinfection and who, therefore, should initiate TDF-containing ART.

20.2. Laboratory monitoring on ART

Two RCTs (DART and HBAC) and two observational studies have assessed laboratory monitoring strategies. The DART study compared a laboratory-driven monitoring strategy (CD4 cell count every 3 months) to a clinically-driven monitoring strategy.(*211*) There was a small but statistically significant difference in mortality and disease progression in favour of the laboratory strategy but only from the third year on ART. HBAC compared clinical monitoring alone to clinical monitoring and the addition of CD4 cell count or CD4 cell count and viral load, both performed every 3 months. In this study, clinical monitoring alone was associated with an increased rate of AIDS-defining events and a trend towards increased mortality. No additional benefit was seen from adding quarterly viral load measurements to CD4 cell count in the first 3 years of ART.(*148*)

The two observational studies which compared immunological and clinical versus virological, immunological and clinical monitoring reported that, in programmes with virological, immunological and clinical monitoring a switch to second-line therapy occurred earlier, more frequently and at higher CD4 counts.(*212*) Three further monitoring trials, all of which are assessing viral load monitoring in different strategies, are progressing in Cameroon, Thailand, and Zambia.(*213–215*)

For NNRTI-containing regimens, symptom-directed laboratory monitoring of liver enzymes is recommended. Symptom-directed monitoring means ordering tests only when the care provider recognizes signs and symptoms of potential ART-related toxicity. For women initiating NVP with a CD4 count of 250–350 cells/mm^3, if feasible, it is recommended (but not required) to monitor hepatic enzymes at weeks 2, 4 and 12 after initiation.

For AZT-containing regimens, haemoglobin (Hb) measurement is recommended before the initiation of AZT and then as indicated by signs/symptoms. Patients receiving AZT-containing regimens and with low body weight and/or low CD4 cell counts are at greater risk of anaemia. These patients should have routine Hb monitoring 1 month after initiating AZT and then at least every 3 months. AZT should not be given if Hb is <7 g/dl.

For TDF-containing regimens, creatinine clearance calculation is recommended, if feasible, before initiation and every 6 months. The inability to perform creatinine clearance is not a barrier to TDF use. Creatinine clearance monitoring is recommended in those with underlying renal disease, of older age groups, and with low body weight or other renal risk factors such as diabetes or hypertension.

There is evidence that individuals taking TDF and a PI/r may experience greater median decline in creatinine clearance than those taking TDF and an NNRTI-based regimen.(*216*) Creatinine clearance should be monitored more closely when TDF is used with a PI/r.

For individuals with HIV/HBV or HIV/HCV coinfection it is recommended to monitor hepatic enzymes at weeks 4 and 12 following ART initiation if feasible.

Table 16. Monitoring ART in those at higher risk of adverse events

ARV drug	Major toxicity	High-risk situations*
d4T	Lipodystrophy Neuropathy Lactic acidosis	Age >40 years CD4 count of <200 cells/mm^3 BMI >25 (or body weight >75kg) Concomitant use with INH or ddI
AZT	Anaemia Neutropaenia	CD4 count of <200 cells/mm^3 BMI <18.5 (or body weight <50 kg) Anaemia at baseline
TDF	Renal dysfunction	Underlying renal disease Age >40 years BMI <18.5 (or body weight <50 kg) Diabetes mellitus Hypertension Concomitant use of a bPI or nephrotoxic drugs
EFV	Teratogenicity	first trimester of pregnancy (do not use EFV)
	Psychiatric illness	Depression or psychiatric disease (previous or at baseline)
NVP	Hepatotoxicity	HCV and HBV coinfection

21. ANNEXES

21.1. Special note on coinfection with HIV and hepatitis C

Hepatitis C (HCV) coinfection is significantly associated with increased risk of death and advanced liver disease in HIV-positive individuals. HIV infection accelerates HCV-related disease progression and mortality (*217–219*) but the reciprocal effect of HCV on the rate of HIV disease progression remains difficult to quantify because of the heterogeneity of study results. A recent meta-analysis showed an increase in the overall risk of mortality but did not demonstrate an increased risk of AIDS-defining events among coinfected patients.(*220*)

A major observational cohort study on the level of toxicities of specific ART regimens used for HIV/HCV coinfection did not find significant differences.(*221*) However, the systematic review on drug-drug interactions prepared for these guidelines found important pharmacological interactions between ribavirin and ABC, ATV, AZT, d4T and ddI that can increase the toxicity risk if these drugs are used concomitantly.(*222–226*)

Many studies also suggest that the sustained viral response rates of HCV therapy in HIV-coinfected individuals are significantly lower than in HCV-monoinfected patients (*227–230*) but others have achieved higher rates in this population.(*231*)

Considering the significant level of uncertainty on these topics and the importance of hepatitis C management in the context of HIV coinfection (an important gap highlighted by the guidelines panel group, particularly the representatives from the people living with HIV community), WHO is planning to revise the recommendations for the prevention and treatment of major HIV-related opportunistic infections and comorbidities, including hepatitis C. Furthermore, it is expected that the 2010 World Health Assembly will establish global policy recommendations for the management of viral hepatitis, which will increase support for an integrated approach to the prevention, treatment and care of HIV/HCV coinfection.

Meanwhile, the initiation of ART in HIV/HCV coinfected people should follow the same principles and recommendations as for its initiation in HIV-monoinfected individuals. However, patients should be closely monitored because of the increased risk of drug toxicities and drug interactions between some ARVs and anti-HCV drugs.

21.2. Dosages of recommended antiretrovirals

Generic name	Dose
Nucleoside reverse transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Didanosine (ddI)	400 mg once daily (>60 kg) 250 mg once daily (≤60 kg)
Emtricitabine (FTC)	200 mg once daily

Generic name	Dose
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (AZT)	250–300 mg twice daily
Nucleotide reverse transcriptase inhibitors (NtRTIs)	
Tenofovir	300 mg once daily[1]
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily[2]
Proteases inhibitors (PIs)	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	600 mg + 100 mg twice daily
Fos-amprenavir + ritonavir (FPV/r)	700 mg + 100 mg twice daily
Indinavir + ritonavir (IDV/r)	800 mg + 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	Fixed Dose Combination tablets (LPV 200 mg / RTV 50 mg) Two tablets (400 mg/200 mg) twice daily[3]
	Considerations for individuals on TB therapy In the presence of rifabutin, no dose adjustment required In the presence of rifampicin; use ritonavir superboosting (LPV 400 mg + RTV 400 mg twice daily) or LPV 800 mg + RTV 200 mg twice daily ,with close clinical and hepatic enzyme monitoring

Generic name	Dose
Saquinavir + ritonavir (SQV/r)	1000 mg + 100 mg twice daily
	Considerations for individuals on TB therapy In the presence of rifabutin, no dose adjustment required In the presence of rifampicin; use ritonavir superboosting (SQV 400 mg + RTV 400 mg twice daily) with close clinical and hepatic enzyme monitoring
Integrase strand transfer inhibitors (INSTIs)	
Raltegravir (RAL)	400 mg twice daily

[1] TDF dosage adjustment for individual with altered creatinine clearance can be considered (using Cockcroft-Gault formula).

Creatinine clearance ≥50 ml/min, 300 mg once daily.

Creatinine clearance 30–49 ml/min, 300 mg every 48 hours.

Creatinine clearance ≥10–29ml/min (or dialysis), 300 mg once every 72–96 hours.

Cockcroft-Gault formula: *GFR = (140-age) x (Wt in kg) x (0.85 if female) / (72 x Cr)*

[2] In the presence of rifampicin, or when patients switch from EFV to NVP, no need for lead-in dose of NVP.

[3] LPV/r can be administered as 4 tablets once daily (i.e. LPV 800 mg + RTV 200 mg once daily) in patients with less than three LPV resistance-associated mutations on genotypic testing. Once-daily dosing is not recommended in pregnant women or patients with more than three LPV resistance-associated mutations.

21.3. Toxicities and recommended drug substitutions

ARV drug	Common associated toxicity	Suggested substitute
TDF	Asthenia, headache, diarrhoea, nausea, vomiting, flatulence Renal insufficiency, Fanconi syndrome Osteomalacia Decrease in bone mineral density Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF	If used in first-line therapy AZT (or d4T if no other choice) If used in second-line therapy Within a public health approach, there is no option If patient has failed AZT/d4T in first-line therapy. If feasible, consider referral to a higher level of care where individualized therapy may be available

ARV drug	Common associated toxicity	Suggested substitute
AZT	Bone marrow suppression: macrocytic anaemia or neutropaenia Gastrointestinal intolerance, headache, insomnia, asthenia Skin and nail pigmentation Lactic acidosis with hepatic steatosis	If used in first-line therapy TDF (or d4T if no other choice) If used in second-line therapy d4T
EFV	Hypersensitivity reaction Stevens-Johnson syndrome Rash Hepatic toxicity Persistent and severe CNS toxicity (depression, confusion) Hyperlipidaemia Male gynaecomastia Potential teratogenicity (first trimester of pregnancy or women not using adequate contraception)	NVP bPI if intolerant to both NNRTIs Triple NRTI if no other choice
NVP	Hypersensitivity reaction Stevens-Johnson syndrome Rash Hepatic toxicity Hyperlipidaemia	EFV bPI if intolerant to both NNRTIs Triple NRTI if no other choice
ATV/r	Indirect hyperbilirubinaemia Clinical jaundice Prolonged PR interval — first degree symptomatic AV block in some patients Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in individuals with haemophilia Nephrolithiasis	LPV/r

ARV drug	Common associated toxicity	Suggested substitute
LPV/r	GI intolerance, nausea, vomiting, diarrhoea Asthenia Hyperlipidaemia (especially hypertriglyceridaemia) Elevated serum transaminases Hyperglycaemia Fat maldistribution Possible increased bleeding episodes in patients with haemophilia PR interval prolongation QT interval prolongation and torsade de pointes	ATV/r

21.4. ARV-related adverse events and recommendations

Table 17. Symptom-directed toxicity management table

Adverse events	Major first-line ARVs	Recommendations
Acute pancreatitis	d4T	Discontinue ART. Give supportive treatment with laboratory monitoring. Resume ART with an NRTI with low pancreatic toxicity risk, such as AZT or TDF.
Drug eruptions (mild to severe, including Stevens-Johnson syndrome or toxic epidermal necrolysis)	NVP, EFV (less commonly)	In mild cases, symptomatic care. EFV rash often stops spontaneously after 3–5 days without need to change ART. If 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 a bPI-based regimen or triple NRTI if no other choice.

Adverse events	Major first-line ARVs	Recommendations
Dyslipidaemia	All NRTIs (particularly d4T) EFV	Consider replacing the suspected ARV
Anaemia and neutropaenia	AZT	If severe (Hb <7.0 g/dl and/or ANC <750 cells/mm^3), replace with an ARV with minimal or no bone marrow toxicity (e.g. d4T or TDF) and consider blood transfusion
Hepatitis	All ARVs (particularly NVP)	If ALT is at more than five times the basal level, discontinue ART and monitor. After resolution, restart ART, replacing the causative drug (e.g . EFV replaces NVP).
Lactic acidosis	All NRTIs (particularly d4T)	Discontinue ART and give supportive treatment. After resolution, resume ART with TDF.
Lipoatrophy and lipodystrophy	All NRTIs (particularly d4T)	Early replacement of the suspected ARV drug (e.g. d4T for TDF or AZT)
Neuropsychiatric changes	EFV	Usually self-limited, without the need to discontinue ART. If intolerable to the patient, replace NVP with EFV or bPI. Single substitution recommended without cessation of ART.
Renal toxicity (renal tubular dysfunction)	TDF	Consider substitution with AZT
Peripheral neuropathy	d4T	Replacement of d4T with AZT, TDF. Symptomatic treatment (amitriptyline, vitamin B6).

21.5. Diagnostic criteria for HIV-related clinical events

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 3 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 6 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 ulcerations (two or more episodes in last 6 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 infections	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)	Reported unexplained 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 1 month	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than 1 month	Not required but confirmed if three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens
Unexplained persistent fever (intermittent or constant and lasting for longer than 1 month)	Reports of fever or night sweats for more than 1 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 37.6 ^{o}C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection

Clinical event	Clinical diagnosis	Definitive diagnosis
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 TB	Chronic symptoms (lasting at least 2 to 3 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)
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 stomatitis, gingivitis or periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, rapid loss of bone and/or soft tissue	Clinical diagnosis

Clinical event	Clinical diagnosis	Definitive diagnosis
Unexplained anaemia (below 8g/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic (more than 1 month) thrombocytopenia (under 50 x 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	Reported unexplained 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 1 month OR reports of fever or night sweats for more than 1 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 ^{o}C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged CXR
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past 3 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

Clinical event	Clinical diagnosis	Definitive diagnosis
Recurrent bacterial pneumonia (this episode plus one or more episodes in last 6 months)	Current episode plus one or more episodes in last 6 months. Acute onset (under 2 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 1 month, or visceral at any site or 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 in swallowing (food and fluids) together with oral candidiasis	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy/histology
Extrapulmonary TB	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, osteitis. Miliary TB: diffuse uniformly distributed small miliary shadows or micronodules on CXR. Discrete cervical lymph node *M. tuberculosis* infection is usually considered a less severe form of extrapulmonary tuberculosis.	*M. tuberculosis* isolation or compatible histology from appropriate site, together with compatible symptoms/signs (if culture/histology is from respiratory specimen there must be other evidence of extrapulmonary disease)

Clinical event	Clinical diagnosis	Definitive diagnosis
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 (retinitis or infection of other organs, excluding liver, spleen and lymph nodes)	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)
CNS toxoplasmosis	Recent onset of a focal neurological abnormality or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single/multiple intracranial mass lesion on neuroimaging (CT or MRI)
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

Clinical event	Clinical diagnosis	Definitive diagnosis
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
Cryptosporidiosis (with diarrhoea lasting more than 1 month)	No presumptive clinical diagnosis	Cysts identified on modified ZN microscopic examination of unformed stool
Chronic isosporiasis	No presumptive clinical diagnosis	Identification of *Isospora*
Disseminated mycosis (coccidiomycosis, histoplasmosis)	No presumptive clinical diagnosis	Histology, antigen detection or culture from clinical specimen or blood culture
Recurrent septicemia (including non-typhoid 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

Clinical event	Clinical diagnosis	Definitive diagnosis
Atypical disseminated leishmaniasis	No presumptive clinical diagnosis	Histology (amastigotes visualized) or culture from any appropriate clinical specimen
HIV-associated nephropathy	No presumptive clinical diagnosis	Renal biopsy
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.

21.6. Grading of selected clinical and laboratory toxicities

Estimating severity grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life- threatening Grade 4
Clinical adverse event NOT identified elsewhere in the table	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, persistent disability or death
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	Mild Grade 1	Moderate Grade 2		Severe Grade 3	Potentially life-threatening Grade 4
Hyperbilirubinaemia	>1.0–1.5 x ULN	>1.5–2.5 x ULN		>2.5–5 x ULN	>5 x ULN
Glucose (fasting)	110–125 mg/dl	126–250 mg/dl		251–500mg/dl	>500 mg/dl
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	–	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
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
Bilirubin	1.1–1.5 X ULN	1.6–2.5 x ULN	2.6–5.0 x ULN		>5 x ULN
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	**Mild** **Grade 1**	**Moderate** **Grade 2**	**Severe** **Grade 3**	**Potentially life-threatening** **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	**Mild** **Grade 1**	**Moderate** **Grade 2**	**Severe** **Grade 3**	**Potentially life-threatening** **Grade 4**
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring O_2 therapy
Urinalysis	**Mild** **Grade 1**	**Moderate** **Grade 2**	**Severe** **Grade 3**	**Potentially life-threatening** **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	**Mild** **Grade 1**	**Moderate** **Grade 2**	**Severe** **Grade 3**	**Potentially life-threatening** **Grade 4**
Fever (oral, >12 hours)	37.7–38.5 ^{0}C OR 100.0–101.5 ^{0}F	38.6–39.5 ^{0}C OR 101.6–102.9 ^{0}F	39.6–40.5 ^{0}C OR 103–105 ^{0}F	>40.5 ^{0}C OR >105 ^{0}F for ≥12 continuous hours

Headache	Mild; no Rx required	Moderate OR non-narcotic analgesia Rx	Severe OR responds to initial narcotic Rx	Intractable
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria, angioedema	Anaphylaxis
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
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25–50%	Normal activity reduced by >50%; cannot work	Unable to care for self

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases, version 1.0 December 2004, clarification August 2009.

NOTE: This clarification includes the addition of Grade 5 toxicity, which is death.

For abnormalities not found elsewhere in the toxicity table, use the information on *Estimating severity grade* in the first column.

21.7. Prevention and Assessment of HIV Drug Resistance

The emergence of HIV drug resistance (HIVDR) is of increasing concern in countries where ART and ARV prophylaxis is widely used, and represents a potential impediment to the achievement of long-term success in treatment outcomes. The rapid or uncontrolled emergence of HIVDR could lead to an increase in therapeutic failures, transmission of resistant virus, and a decrease in therapeutic options, treatment programme effectiveness and survival. Implementing programme elements that minimize the emergence of HIVDR, including optimizing access to ART, supporting appropriate ART prescribing and adherence, and ensuring adequate and continuous drug supplies, is essential for preserving the efficacy of the limited number of ARV drugs available in many countries.[i] Transmission of resistant virus is minimized through support for prevention programmes for HIV positive individuals.

To guide these interventions, WHO, together with its partners in The Global HIV Drug Resistance Network (HIVResNet), developed and encourages countries to adopt an HIVDR prevention and assessment strategy. The goal of the strategy, coordinated at country level by a national HIVDR working group, is to support development of evidence to inform programme actions that maintain the effectiveness of ART regimens and limit HIVDR transmission. The elements, which comprise an important public health tool to support national, regional and global ART scale-up efforts, include:

Regular monitoring of key early warning indicators in ART sites that may be programmatically improved to minimize the emergence of HIVDR;

Monitoring surveys to assess the emergence of HIVDR and associated factors in cohort(s) of treated patients 12 months after ART initiation in sentinel ART sites; and

Surveillance for transmitted drug-resistant HIV-1 among individuals newly infected.

Further information on and resources to support the WHO HIVDR prevention and assessment strategy are available at http://www.who.int/hiv/drugresistance/.

i Note that WHO does not recommend routine HIV drug resistance testing for individual patient management in settings where other basic laboratory measurements such as CD4 and HIV VL are not yet available.

21.8. Special Note on Antiretroviral Pharmacovigilance

Background

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.[ii] It incorporates and provides training in the identification of adverse reactions, data collection, processing, analysis and reporting. Pharmacovigilance is a key component of comprehensive patient care and the safe use of medicines. Adverse events and severe adverse events, both pre and post marketing, have been reported with all antiretrovirals. Not monitoring, understanding and managing these events can result in poor adherence, treatment failure and reduce confidence in ART by both PLHIV and care providers.

Objectives of pharmacovigilance

The main objectives of pharmacovigilance in antiretroviral programs are to maximize patient safety and the outcomes of public health programs, identify early warning signs (signals) of adverse reactions to drugs used in the management of HIV infection, monitor the safety of antiretrovirals in specific groups including pregnant women and in children, identify drug-drug interactions and quantify the rates of these events and report them to health authorities/ clinicians. Pharmacovigilance programs also provide methodological training and address issues related to unregulated prescribing, drug quality control and counterfeit drugs.

Pharmacovigilance in resource limited settings

In resource limited settings, antiretroviral pharmacovigilance is poorly developed but is critical because of factors unique to these settings. There has been rapid scale-up of largely generic antiretroviral therapy drug combinations not commonly used in well-resource settings. Pharmacovigilance is required not only for chronic antiretroviral therapy but also for the antiretrovirals used for the prevention of mother to child transmission of HIV. There are distinct co-comorbidities (tuberculosis, malaria) and drug-drug interactions.

Methodology

There are two main methods of monitoring, cohort event monitoring (CEM) and spontaneous reporting. A third method is consumer reporting, whereby a report of a suspected adverse drug reaction is initiated by the drug consumer.

In spontaneous reporting systems, suspected adverse drug events are voluntarily submitted by health professionals and pharmaceutical manufacturers to the national regulatory authority. Spontaneous reporting is the most common form of pharmacovigilance and is the core activity of national pharmacovigilance centres participating in the WHO international drug monitoring program. It requires fewer human and financial resources than CEM, and is likely to be the method used in most resource limited settings in the foreseeable future. The system has limitations. The success or failure of a spontaneous reporting system depends on the active participation of reporters. Under reporting is common in all counties, irrespective of their

ii The safety of medicines in public health programmes: Pharmacovigilance an essential tool (WHO, 2006).

resources. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an adverse drug reaction attributable to a product, or its safety in relation to a comparator.[iii]

CEM is a prospective observational cohort study of adverse events associated with one or more medicines. In CEM, all adverse events occurring in a patient taking antiretroviral are collected irrespective of causality or relationship the antiretrovirals. Advantages of CEM (over spontaneous reporting) include the ability to produce rates, rapid results, early detection of signals, fewer missing data and less reporting bias. However, CEM is requires more resources than spontaneous reporting.

WHO and partners are preparing a toolkit for countries wishing incorporate pharmacovigilance into their antiretroviral programs. In the mean time, the following resources are available:

- Pharmacovigilance for antiretrovirals home page
  http://www.who.int/hiv/topics/pharmacovigilance/en/index.html
- A practical handbook on the pharmacovigilance of antiretroviral medicines (WHO 2009)
  http://www.who.int/hiv/topics/pharmacovigilance/arv_pharmacovigilance_handbook.pdf
- Pharmacovigilance for antiretroviral in resource limited settings (WHO 2007)
  http://www.who.int/medicines/publications/PhV_for_antiretrovirals.pdf
- The safety of medicines in public health programmes: Pharmacovigilance an essential tool (WHO 2006)
  www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf
- The importance of pharmacovigilance: Safety Monitoring of medicinal products
  http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf

iii Meyboom RHB, Egberts ACG, Gribnau FWJ, Hekster YA. Pharmacovigilance in perspective. *Drug Safety* 1999; 21(6): 429-447.

21.9 GRADE evidence tables

The following tables present profiles of the evidence considered for the recommendations made in these guidelines.

For further information on the methodology of the GRADE process see *The Conchrane handbook for systematic reviews of interventions*, available at http://cochrane-handbook.org.

When to start ART

Authors: Nandi L Siegfried, Ololaken Uthman, George W Rutherford
Date: 11 Sep 2009
Question: Early ART versus standard or deferred ART (CD4 ≤200 or CD4 ≤250 cells/μl) for asymptomatic, HIV-infected, treatment-naive adults.
Bibliography: Siegfried NL, Uthman O, Rutherford GW. Optimal time of initiation for asymptomatic, HIV-infected, treatment- naive adults. Cochrane Database of Systematic Reviews.

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsis-tency	Indirect-ness	Impreci-sion	Other consider-ations	Early ART versus standard or deferred ART (CD4 ≤200 or CD4 ≤250 ells/μl)	Control	Relative (95% CI)	Absolute	Quality	Importance
Death												
2	Random-ized trials	No serious limitations[1]	No serious inconsis-tency	No serious indirectness	No serious imprecision	Reporting bias[2]	6/539 (1.1%)	24/526 (4.6%)	RR 0.26 (0.11 to 0.62)	34 fewer per 1000 (from 17 fewer to 41 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Tuberculosis												
2	Random-ized trials	No serious limitations[1]	No serious inconsis-tency	No serious indirectness	No serious imprecision	Reporting bias[2]	19/539 (3.5%)	36/526 (6.8%)	RR 0.54 (0.26 to 1.12)	31 fewer per 1000 (from 51 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL

Disease progression measured by opportunistic disease (follow-up mean 18 months; opportunistic disease events)												
1	Random-ized trials	No serious limitations[1]	No serious inconsis-tency	Serious[3]	No serious imprecision	Reporting bias[2]	1/131 (0.8%)	3/118 (2.5%)	RR 0.30 (0.03 to 2.85)	18 fewer per 1000 (from 25 fewer to 44 more)	⊕⊕OO LOW	CRITICAL
Any Grade 3 or 4 adverse event – awaiting confirmation of grading and frequency of SAE												
												CRITICAL
Sexual transmission – not measured												
0	-	-	-	-	-				-	-	-	IMPORTANT
Immunological response – not measured												
0	-	-	-	-	-				-	-	-	IMPORTANT
Adherence/tolerance/retention – not measured												
0	-	-	-	-	-				-	-	-	IMPORTANT
HIV drug resistance – not measured												
0	-	-	-	-	-				-	-	-	IMPORTANT
Virological response – not measured												
0	-	-	-	-	-				-	-	-	IMPORTANT

[1] The SMART study is a post hoc analysis of a subset of a larger trial.

[2] As the SMART subset is a post hoc analysis there may be other trials which did not conduct or publish similar analyses of potential subsets within the original trials. This is a form of publication bias and we have downgraded the results accordingly.

[3] This result is a post hoc subset analysis from only one trial and the evidence is therefore not directly able to answer the outcome of disease progression.

What ART to start

Authors: George Rutherford, Alicen Spauldin
Date: 8 Oct 2009
Question: Should EFV vs NVP be used for initial ART? (Randomized clinical trials)
Settings: Multiple locations
Bibliography:

1. Ayala Gaytan JJ, de la Garza ERZ, Garcia MC, Chavez SBV. Nevirapine or efavirenz in combination with two nucleoside analogues in HIV infected antiretroviral naive patients. *Med Intern Mex* 2004;20:24. 2. Manosuthi W, Sungkanuparph S, Tantanathip P, Lueangniyomkul A, Mankatitham W, Prasithsirskul W, Buraptarawong S, Thongyen S, Likanonsakul S, Thawornwa U, Prommool V, Kuxrungtham K, 2NR Study Team. A randomized trial comparing plasma drug concentrations and efficacies between 2 nonnucleoside reverse-transcriptase inhibitor-based regimens in HIV-infected patients receiving rifampicin: the N2R Study. *Clin Infect Dis* 2009;48:1752-9. 3. Núñez M, Soriano V, Martín-Carbonero L, Barrios A, Barreiro P, Blanco F, García-Benayas T, González-Lahoz J. SENC (Spanish Efavirenz vs. Nevirapine Comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials* 2002;3:186-94. 4. Sow PG, Badiane M, Diallo PD, Lo I, Ndiaye B, Gaye AM. *Efficacy and safety of lamivudine+zidovudine+efavirenz and lamivudine+zidovudine+névirapine in treatment HIV1 infected patients. A rétrospective cross study analysis* [Abstract CDB0584]. XVI International AIDS Conference, Toronto, Canada, 13–18 August 2006. 5. van den Berg-Wolf M, Hullsiek KH, Peng G, Kozal MJ, Novak RM, Chen L, Crane LR, Macarthur RD; CPCRA 058 Study Team, the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA), and The International Network for Strategic Initiative in Global HIV Trials (INSIGHT). Virologic, immunologic, clinical, safety, and resistance outcomes from a long-term comparison of efavirenz-based versus nevirapine-based antiretroviral regimens as initial therapy in HIV-1-infected persons. *HIV Clin Trials* 2008;9:324-36. 6. van Leth F, Kappelhoff BS, Johnson D, Losso MH, Boron-Kaczmarska A, Saag MS, Hall DB, Leith J, Huitema AD, Wit FW, Beljnen JH, Lange JM; 2NN Study Group. Pharmacokinetic parameters of nevirapine and efavirenz in relation to antiretroviral efficacy. *AIDS Res Hum Retroviruses* 2006;22:232-39.

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	EFV	NVP	Relative (95% CI)	Absolute		
Mortality (follow-up 2 studies at 48 weeks, 1 study at 65 months)												
3	Randomized trials	No serious limitations[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	29/582 (5%)	33/575 (5.7%)	RR 0.89 (0.5 to 1.57)	6 fewer per 1000 (from 29 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical response (follow-up 2 studies at 48 weeks, 1 study at 65 months)												
3	Randomized trials	No serious limitations[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	44/541 (8.1%)	34/532 (6.4%)	RR 1.31 (0.78 to 2.2)	20 more per 1000 (from 14 fewer to 77 more)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events (follow-up 2 studies at 48 weeks, 1 study at 65 months)												
4	Randomized trials	No serious limitations[1]	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None[4]	96/612 (15.7%)	140/603 (23.2%)	RR 0.68 (0.54 to 0.86)	74 fewer per 1000 (from 33 fewer to 107 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Virological response (follow-up 2 studies at 48 weeks, 1 study at 65 months)												
5	Randomized trials	No serious limitations[1]	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None[4]	508/643 (79%)	500/639 (78.2%)	RR 0.99 (0.91 to 1.09)	8 fewer per 1000 (from 70 fewer to 70 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adherezce/tolerability/retention (follow-up 4 studies at 48 weeks, 1 study at 65 months, 1 study did not report follow-up period)												
6	Randomized trials	No serious limitations[1]	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None[4]	335/678 (49.4%)	304/674 (45.1%)	RR 1.11 (0.95 to 1.28)	50 more per 1000 (from 23 fewer to 126 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Immunological response (follow-up 4 studies at 48 weeks, 1 study at 65 months, 1 study at 6 months; better indicated by higher values)												
5	Randomized trials	No serious limitations[1]	No serious inconsistency	No serious indirectness[2]	Serious[5]	None[4]	643	639	-	MD 3.95 higher (11.58 lower to 19.48 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up median 65 months)												
1	Randomized trials	Serious[1,6]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	32/111 (28.8%)	49/117 (41.9%)	RR 0.69 (0.48 to 0.99)	130 fewer per 1000 (from 4 fewer to 218 fewer)	⊕⊕OO LOW	IMPORTANT
Sexual transmission of HIV not reported												
0	-	-	-	-	-	None	0/0 (0%)	0/0 (0%)	-	-		

1 4 of 6 studies were open-label; 1 of the remaining studies did not provide sufficient information on blinding (Sow) and the other was blinded (van den Berg-Wolf) but studies were not downgraded based on these facts.

2 1 study (van den Berg et al.) looked at multiple indirect comparisons. Also, only 1 of 6 studies was only conducted in a developed country setting (Manosuthi).

3 Number of events <300 and/or confidence intervals include potential harm and benefit.

4 1 of 6 studies were industry-funded (van Leth et al.), while 1 of 6 studies had a funding source that was unclear.

5 None of the included studies provided standard deviations for the mean outcome so the same estimated SD value was used for all studies.

6 Only 1 study reported on drug resistance (van den Berg-Wolf et al.) , suggesting selective reporting.

Authors: George Rutherford, Alicen Spaulding
Date: 8 Oct 2009
Question: Should EFV vs NVP be used for initial ART? (observational studies)
Settings: Multiple locations
Bibliography: 1. Annan T, Mandalia S, Bower M, Gazzard B, Nelson M. *The effect of year of treatment and nucleoside analogue backbone on durability of NNRTI based regimens* [Abstract WePe12.2C03]. 3rd Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, 24-27 July 2005. 2. Aranzabal L, Casado JL, Moya J, Quereda C, Diz S, Moreno A, Moreno L, Antela A, Perez-Elias MJ, Dronda F, Marín A, Hernandez-Ranz F, Moreno A, Moreno S. Influence of liver fibrosis on highly active antiretroviral therapy-associated hepatotoxicity in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis* 2005;40:588-93. 3. Aurpibul L, Puthanakit T, Lee B, Mangklabruks A, Sirisanthana T, Sirisanthana V. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther* 2007;12:1247-54. 4. Bannister WP, Ruiz L, Cozzi-Lepri A, Mocroft A, Kirk O, Staszewski S, Loveday C, Karlsson A, Monforte A, Clotet B, Lundgren JD. Comparison of genotypic resistance profiles and virological response between patients starting nevirapine and efavirenz in EuroSIDA. *AIDS* 2008;22:367-76. 5. Berenguer J, Bellon JM, Miralles P, Alvarez E, Castillo I, Cosin J, Lopez JC, Sanchez Conde M, Padilla B, Resino S. Association between exposure to nevirapine and reduced liver fibrosis progression in patients with HIV and hepatitis C virus coinfection. *Clin Infect Dis* 2008;46:137-43. 6. Boulle A, Orrel C, Kaplan, Van Cutsem G, McNally M, Hilderbrand K, Myer L, Egger M, Coetzee D, Maartens G, Wood R. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. *Antivir Ther* 2007;12:753-60. 7. Boulle A, Van Cutsem G, Cohen K, Hilderbrand K, Mathee S, Abrahams M, Goemaere E, Coetzee D, Maartens GT. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008;300:530-9. 8. Braithwaite RS, Kozal MJ, Chang CC, Roberts MS, Fultz SL, Goetz MB, Gibert C, Rodriguez-Barradas M, Mole L, Justice AC. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. *AIDS* 2007;21:1579-89. 9. de Beaudrap P, Etard JF, Guèye FN, Guèye M, Landman R, Girard PM, Sow PS, Ndoye I, Delaporte E; ANRS 1215/1290 Study Group. Long-term efficacy and tolerance of efavirenz- and nevirapine-containing regimens in adult HIV type 1 Senegalese patients. *AIDS Res Hum Retroviruses* 2008;24:753-60. 10. Ena J, Amador C, Benito C, Fenoll V, Pasquau F. Risk and determinants of developing severe liver toxicity during therapy with nevirapine-and efavirenz-containing regimens in HIV-infected patients. *Int J STD AIDS* 2003;14:776-81. 11. George C, Yesoda A, Jayakumar B, Lal L. A prospective study evaluating clinical outcomes and costs of three NNRTI-based HAART regimens in Kerala, India. *J Clin Pharm Ther* 2009;34:33-40. 12. Hartmann M, Witte S, Brust J, Schuster D, Mosthaf F, Procaccianti M, Rump JA, Klinker H, Petzoldt D. Comparison of efavirenz and nevirapine in HIV-infected patients (NEEF Cohort). *Int J STD AIDS* 2005;16:404-9. 13. Keiser P, Nassar N, White C, Koen G, Moreno S. Comparison of nevirapine- and efavirenz-containing antiretroviral regimens in antiretroviral-naïve patients: a cohort study. *HIV Clin Trials* 2002;3:296-303. 14. Madec Y, Laureillard D, Pinoges L, Fernandez M, Prak N, Ngeth C, Moeung S, Song S, Balkan S, Ferradini

L, Quillet C, Fontanet A. Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. *AIDS* 2007;21:351-9. 15. Manosuthi W, Sungkanuparph S, Vibhagool A, Rattanasiri S, Thakkinstian A. Nevirapine- versus efavirenz-based highly active antiretroviral therapy regimens in antiretroviral-naive patients with advanced HIV infection. *HIV Med* 2004;5:105-9. 16. Manosuthi W, Mankatitham W, Lueangniyomkul A, Chimsuntorn S, Sungkanuparph S. Standard-dose efavirenz vs. standard-dose nevirapine in antiretroviral regimens among HIV-1 and tuberculosis co-infected patients who received rifampicin. *HIV Med* 2008;9:294-99. 17. Martín-Carbonero L, Núñez M, González-Lahoz J, Soriano V. Incidence of liver injury after beginning antiretroviral therapy with efavirenz or nevirapine. *HIV Clin Trials* 2003;4:115-20. 18. Matthews GV, Sabin CA, Mandalia S, Lampe F, Phillips AN, Nelson MR, Bower M, Johnson MA, Gazzard BG. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. *AIDS* 2002;16:53–61. 19. Nachega JB, Hislop M, Dowdy DW, Gallant JE, Chaisson RE, Regensberg L, Maartens G. Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes in Southern African adults. *AIDS* 2008;22:2117-25. 20. Palmon R, Koo BC, Shoultz DA, Dieterich DT. Lack of hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. *J Acquir Immune Defic Syndr* 2002;29:340-5. 21. Patel AK, Pujari S, Patel K, Patel J, Shah N, Patel B, Gupte N. Nevirapine versus efavirenz based antiretroviral treatment in naive Indian patients: comparison of effectiveness in clinical cohort. *J Assoc Physicians India* 2006;54:915-18. 22. Sanne I, Mommeja-Marin H, Hinkle J, Bartlett JA, Lederman MM, Maartens G, Wakeford C, Shaw A, Quinn J, Gish RG, Rousseau F. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis* 2005; 191:825-9. 23. Shipton LK, Wester CW, Stock S, Ndwapi N, Gaolathe T, Thior I, Avalos A, Moffat HJ, Mboya JJ, Widenfelt E, Essex M, Hughes MD, Shapiro RL. Safety and efficacy of nevirapine- and efavirenz-based antiretroviral treatment in adults treated for TB-HIV co-infection in Botswana. *Int J Tuberc Lung Dis* 2009;13:360-6. 24. Varma J, Nateniyom S, Akksilp S, Mankatittham W, Sirinak C, SattayawuthipongW, Burapat C, Kittikraisak W, Monkongdee P, Cain KP, Wells CD, Tappero JW. HIV care and treatment factors associated with survival during TB treatment in Thailand: an observational study. *BMC Infect Dis* 2009;9:42.

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	EFV	NVP	Relative (95% CI)	Absolute	Quality	Importance
Mortality (observational)												
5	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	270/2899 (9.3%)	108/2542 (4.2%)	RR 1.47 (0.67 to 3.22)	20 more per 1000 (from 14 fewer to 94 more)	⊕⊕OO LOW	CRITICAL
Serious adverse events (observational)												
14	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	256/3066 (8.3%)	373/3281 (11.4%)	RR 0.7 (0.49 to 1.01)	34 fewer per 1000 (from 58 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Virological response (observational)												
11	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	4023/6661 (60.4%)	3263/4731 (69%)	RR 1.03 (0.92 to 1.15)	21 more per 1000 (from 55 fewer to 103 more)	⊕⊕OO LOW	CRITICAL
Adherence/tolerability/retention (observational)												
5	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	3791/4784 (79.2%)	1894/2635 (71.9%)	RR 1.11 (0.94 to 1.32)	79 more per 1000 (from 43 fewer to 230 more)	⊕⊕OO LOW	CRITICAL
Immunological response (observational) (Better indicated by lower values)												
4	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision[1]	None	1523	1566	-	MD 7.51 higher (0.7 lower to 15.73 higher)	⊕⊕OO LOW	IMPORTANT

[1] None of the included studies provided standard deviations for the mean outcome so the same estimated SD value was used for all studies.

Authors: George Rutherford, Alicen Spaulding
Date: 8 Oct 2009
Question: Should TDF vs ABC be used for initial ART? (randomized clinical trials)
Settings: Multiple locations
Bibliography: 1. Sax P, Tierney C, Collier A, Fischl M, Godfrey C, Jahed N, Droll K, Peeples L, Myers L, Thal G, Rooney J, Ha B, Woodward W, Daar E. *ACTG 5202: shorter time to virologic failure (VF) with abacavir/lamivudine (ABC/3TC) than tenofovir/emtricitabine (TDF/FTC) as part of combination therapy in treatment-naïve subjects with screening HIV RNA ≥100,000 c/mL* [Abstract THAB0303]. XVII International Conference on AIDS, Mexico City, August 3-8, 2008. 2. Smith KY, Patel P, Fine D, Bellos N, Sloan L, Lackey P, Kumar PN, Sutherland-Phillips DH, Vavro, C, Yau L, Wannamaker P, Shaefer MS, HEAT Study Team. Randomized, double-blind, placebo-matched, multicenter trial of abacivr/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS* 2009; Jul 31;23(12):1547-56.

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TDF	ABC	Relative (95% CI)	Absolute		
Mortality – not reported												
0	-	-	-	-	-	None	0/0 (0%)	0/0 (0%)	-	-		
Clinical response (follow-up mean 96 weeks)												
1	Randomized trials	No serious limitations	No serious inconsistency	Serious[1]	Serious[2]	None[3]	1/345 (0.3%)	0/343 (0%)	RR 2.98 (0.12 to 72.96)	0 more per 1000 (from 0 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up mean 96 weeks)												
1	Randomized trials	No serious limitations	No serious inconsistency	Serious[1]	No serious imprecision	None[3]	97/345 (28.1%)	103/343 (30%)	RR 0.94 (0.74 to 1.18)	18 fewer per 1000 (from 78 fewer to 54 more)	⊕⊕⊕O MODERATE	CRITICAL

Virological response (follow-up 1 study at 48, 1 study at 96 weeks)												
2	Randomized trials	No serious limitations	No serious inconsistency[4]	Serious[1]	No serious imprecision	None[3]	550/744 (73.9%)	533/741 (71.9%)	RR 1.03 (0.95 to 1.11)	22 more per 1000 (from 36 fewer to 79 more)	⊕⊕⊕O MODERATE	CRITICAL
Adherence/tolerability/retention (follow-up mean 96 weeks)												
1	Randomized trials	No serious limitations	No serious inconsistency	Serious[1]	No serious imprecision	None[3]	221/345 (64.1%)	234/343 (68.2%)	RR 0.94 (0.84 to 1.05)	41 fewer per 1000 (from 109 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
Immunological response (follow-up mean 96 weeks; Better indicated by higher values)												
1	Randomized trials	No serious limitations	No serious inconsistency	Serious[1]	Serious[2]	None[3]	345	343	-	MD 3 higher (12.69 lower to 18.69 higher)	⊕⊕OO LOW	IMPORTANT
Drug resistance – not reported												
0	-	-	-	-	-	None	0/0 (0%)	0/0 (0%)	-	-		
Sexual transmission of HIV – not reported												
0	-	-	-	-	-	None	0/0 (0%)	0/0 (0%)	-	-		

[1] Both studies looked at the indirect basic comparison of TDF + FTC vs. ABC + 3TC-containing regimens. One study was conducted only in developed country settings (Smith); the final study did not report a location for the study.

[2] Number of events <300 and/or confidence intervals include potential harm and benefit.

[3] One study was industry-funded (Smith et al.) while the source of funding for the other (Sax et al) was unclear; studies were not downgraded based on these facts.

[4] Treatment failure in high-PVL group (viral load ≥100 000 copies/ml) inconsistent with findings from a meta-analysis (Pappa et al 2008) of patients starting ABC + 3TC-containing regimens in which patients with HIV-1 RNA levels of <100 000 copies/ml and ≥100 000 copies/ml had similar experiences and that between 87% and 95% did not experience virological failure.

Authors: George Rutherford, Alicen Spaulding
Date: 8 Oct 2009
Question: Should TDF vs (d4T or AZT) be used for initial ART? (randomized clinical trials)
Settings: Multiple locations
Bibliography: 1. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD, Coakley DF, Lu B, Toole JJ, Cheng AK; 903 Study Group. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA* 2004;292:191-201. 2. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, Lu B, McColl D, Chuck S, Enejosa J, Toole JJ, Cheng AK; Study 934 Group. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006;354(3):251-60. 3. Rey D, Hoen B, Chavanet P, Schmitt MP, Hoizey G, Meyer P, Peytavin G, Spire B, Allavena C, Diemer M, May T, Schmit JL, Duong M, Calvez V, Lang JM. High rate of early virological failure with the once-daily tenofovir/lamivudine/nevirapine combination in naive HIV-1-infected patients. *J Antimicrob Chemother* 2009;63:380-8

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TDF	(d4T or ZDV)	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up mean 144 weeks)												
1	Randomized trials	Serious[1,2]	No serious inconsistency	No serious indirectness[3]	Serious[4]	None	6/303 (2%)	5/299 (1.7%)	RR 1.18 (0.37 to 3.84)	3 more per 1000 (from 11 fewer to 47 more)	⊕⊕OO LOW	CRITICAL
Clinical response – not reported												
0	-	-	-	-	-	none	0/0 (0%)	0/0 (0%)	-	-		
Severe adverse events (follow-up 1 study at 36 weeks, 1 study at 48 weeks, 1 study at 144 weeks)												
3	Randomized trials	No serious limitations[5]	No serious inconsistency	No serious indirectness[3]	No serious imprecision	None[6]	250/591 (42.3%)	247/595 (41.5%)	OR 1.04 (0.81 to 1.34)	10 more per 1000 (from 50 fewer to 72 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Virological response (follow-up 1 study at 36 weeks, 1 study at 48 weeks, 1 study at 144 weeks)												
3	Randomized trials	No serious limitations[2]	No serious inconsistency	No serious indirectness[3]	No serious imprecision	None[6]	384/595 (64.5%)	384/593 (64.8%)	RR 1 (0.76 to 1.3)	0 fewer per 1000 (from 155 fewer to 194 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adherence/tolerability/retention (follow-up 1 study at 36 weeks, 1 study at 48 weeks, 1 study at 144 weeks)												
3	Randomized trials	Serious[5]	No serious inconsistency	No serious indirectness[3]	No serious imprecision	None[6]	445/591 (75.3%)	400/597 (67%)	RR 1.13 (1.05 to 1.21)	87 more per 1000 (from 34 more to 141 more)	⊕⊕⊕O MODERATE	CRITICAL
Immunological response (follow-up 1 study at 48 weeks, 1 study at 144 weeks)												
2	Randomized trials	No serious limitations[2]	No serious inconsistency	No serious indirectness[3]	Serious[4,7]	None[6]	559	558	-	MD 5.88 higher (45.08 lower to 56.84 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up 1 study at 36 weeks, 1 study at 144 weeks)												
2	Randomized trials	No serious limitations[2]	No serious inconsistency	No serious indirectness[3]	Serious[4]	None[6]	18/335 (5.4%)	2/338 (0.6%)	RR 6.12 (1.43 to 26.15)	30 more per 1000 (from 3 more to 149 more)	⊕⊕⊕O MODERATE	IMPORTANT
Sexual transmission of HIV – not reported												
0	-	-	-	-	-	None	0/0 (0%)	0/0 (0%)	-	-		

1 Only 1 of 3 studies reported on mortality (Gallant et al), suggesting selective reporting.

2 2 studies of 3 were open-label (Gallant et al and Rey et al) but studies were not downgraded on this basis.

3 1 study of 3 was an indirect comparison of TDF/FTC/EFV vs. ZDV/3TC/EFV (Gallant et al) and 2 studies of 3 (Gallant et al, Rey et al) were conducted only in developed country settings, but studies were not downgraded based on these facts.

4 Number of events <300 and/or confidence intervals include potential harm and benefit.

5 Assessment of adherence/retention/tolerability or assessment of adverse events may be subject to bias in an open-label study, so downgraded for this outcome.

6 All 3 studies were industry-funded; they were not downgraded for this, however, as study drug did not show benefit so less concern for reporting bias.

7 None of the included studies provided standard deviations for the mean outcome so the same estimated SD value was used for all studies.

Authors: George Rutherford, Alicen Spaulding
Date: 8 Oct 2009
Question: Should TDF vs (d4T or AZT) be used for initial ART? (observational studies)
Settings: Multiple locations
Bibliography: 1. Mocroft A, Phillips AN, Ledergerber B, Katlama C, Chiesi A, Goebel FD, Knysz B, Antunes F, Reiss P, Lundgren JD. Relationship between antiretrovirals used as part of a cART regimen and CD4 cell count increases in patients with suppressed viremia. *AIDS* 2006;20:1141-50.

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	TDF	(d4T or AZT)	Relative (95% CI)	Absolute		
Immunological response (observational) (Better indicated by higher values)												
2	Observational studies	No serious limitations[1]	No serious inconsistency	No serious indirectness	No serious imprecision[2]	None	3618	20377	-	MD 6.33 lower (22.5 lower to 9.84 higher)	⊕⊕OO LOW	IMPORTANT

[1] This is from 1 study but with 2 comparisons.

[2] None of the included studies provided standard deviations for the mean outcome so the same estimated SD value was used for all studies.

Authors: George Rutherford, Alicen Spaulding
Date: 8 Oct 2009
Question: Should AZT vs d4T be used for initial ART? (randomized clinical trials)
Settings: Multiple locations
Bibliography:

1. Carr A, Chuah J, Hudson J, et al. A randomised, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo I study. *AIDS* 2000;14:1171-80. 2. Eron JJ Jr, Murphy RL, Peterson D, Pottage J, Parenti DM, Jemsek J, Swindells S, Sepulveda G, Bellos N, Rashbaum BC, Esinhart J, Schoellkopf N, Grosso R, Stevens M. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II). *AIDS* 2000;14:1601-10. 3. French M, Amin J, Roth N, Carr A, Law M, Emery S, Drummond F, Cooper D; OzCombo 2 investigators. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 Infection: the OzCombo 2 study. *HIV Clin Trials* 2002;3:177-85. 4. Gathe J Jr, Badaro R, Grimwood A, Abrams L, Klesczewski K, Cross A, McLaren C. Antiviral activity of enteric-coated didanosine, stavudine, and nelfinavir versus zidovudine plus lamivudine and nelfinavir. *J Acquir Immune Defic Syndr* 2002;31:399-403. 5. Geijo Martínez MP, Maciá Martínez MA, Solera Santos J, Barberá Farré JR, Rodríguez Zapata M, Marcos Sánchez F, Martínez Alfaro E, Cuadra García-Tenorio F, Sanz Moreno J, Moreno Mendaña JM, Beato Pérez JL, Sanz Sanz J; GECMEI. Ensayo clínico comparativo de eficacia y seguridad de cuatro pautas de tratamiento antirretroviral de alta eficacia (TARGA) en pacientes con infección por VIH avanzada. *Rev Clin Esp* 2006;206:67-76. 6. Kumar PN, Rodriguez-French A, Thompson MA, Tashima KT, Averitt D, Wannamaker PG, Williams VC, Shaefer MS, Pakes GE, Pappa KA, ESS40002 Study Team. A prospective, 96-week study of the impact of Trizivir, Combivir/nelfinavir and lamivudine/stavudine/nelfinavir on lipids, metabolic paramerters and efficacy in antiretorviral-naïve patients: effect of sex and ethnicity. *HIV Med* 2006;7:85-98. 7. Robbins GK, De Gruttola V, Shafer RW, Smeaton LM, Snyder SW, Pettinelli C, Dubé MP, Fischl MA, Pollard RB, Delapenha R, Gedeon L, van der Horst C, Murphy RL, Becker MI, D'Aquila RT, Vella S, Merigan TC, Hirsch MS; AIDS Clinical Trials Group 384 Team. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349:2293-303. 8. Squires KE, Gulick R, Tebas P, Santana J, Mulanovich V, Clark R, Yangco B, Marlowe SI, Wright D, Cohen C, Cooley T, Mauney J, Uffelman K, Schoellkopf N, Grosso R, Stevens M. A comparison of stavudine plus lamivudine versus zidovudine plus lamivudine in combination with indinavir in antiretroviral naive individuals with HIV infection: selection of thymidine analog regimen therapy (START I). *AIDS* 2000;14:1591-600. 9. Li T, Dai Y, Kuang J, Jiang J, Han Y, Qiu Z, Xie J, Zuo L, Li Y. Three generic nevirapine-based antiretroviral treatments in Chinese HIV/AIDS patients: multicentric observation cohort. *PLoS One* 2008;3:e3918.

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ZDV	d4T	Relative (95% CI)	Absolute		
Mortality (follow-up 3 studies at 48 weeks, 1 study at 52 weeks, 1 study at 96 weeks 1)												
6	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[3]	Serious[4]	Reporting bias[5]	3/593 (0.5%)	5/586 (0.9%)	RR 0.74 (0.18 to 2.93)	2 fewer per 1000 (from 7 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
Clinical response (follow-up 3 studies at 48 weeks, 2 studies at 52 weeks)												
7	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[5]	8/360 (2.2%)	6/361 (1.7%)	RR 1.26 (0.46 to 3.45)	4 more per 1000 (from 9 fewer to 41 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks)												
9	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[5]	137/680 (20.1%)	169/685 (24.7%)	RR 0.85 (0.71 to 1.02)	37 fewer per 1000 (from 72 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
Virological response (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks, 1 study at 96 weeks)												
10	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[5]	396/771 (51.4%)	409/768 (53.3%)	RR 0.97 (0.89 to 1.07)	16 fewer per 1000 (from 59 fewer to 37 more)	⊕⊕OO LOW	CRITICAL
Adherence/tolerability/retention (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks, 1 study at 96 weeks, 1 study at 144 weeks)												
12	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[5]	632/1081 (58.5%)	585/1078 (54.3%)	RR 1.08 (0.97 to 1.2)	43 more per 1000 (from 16 fewer to 109 more)	⊕⊕OO LOW	CRITICAL

Immunological response (follow-up 4 studies at 48 weeks, 3 studies at 52 weeks, 1 study at 96 weeks; Better indicated by higher values)												
10	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[3]	No serious imprecision	Reporting bias[5]	771	768	-	MD 9.61 lower (36.82 lower to 17.6 higher)	⊕⊕OO LOW	IMPORTANT
Drug resistance (follow-up at 96 weeks)												
1	Randomized trials	Serious[2,6]	No serious inconsistency	Serious[3]	Serious[4]	None	10/91 (11%)	6/83 (7.2%)	RR 1.52 (0.58 to 4)	38 more per 1000 (from 30 fewer to 217 more)	⊕OOO VERY LOW	IMPORTANT
Sexual transmission of HIV – not reported												
0	-	-	-	-	-	None	0/0 (0%)	0/0 (0%)	-	-		

1 Separate comparison arms from 3 studies (Carr et al, French et al, Robbins et al) contributed more than once for a number of outcomes. There were 9 studies in total.

2 6 of 9 studies were open-label studies and some studies had large rates of loss to follow-up, but studies were not downgraded based on these facts.

3 5 of 9 studies looked at indirect comparisons of drug regimens.

4 Number of events <300 and/or confidence intervals include potential harm and benefit.

5 7 of 9 studies were industry-funded, although some were funded simultaneously by competitors.

6 Only 1 study (Kumar et al) reported on drug resistance, suggesting selective reporting.

Authors: George Rutherford, Alicen Spaulding
Date: 8 Oct 2009
Question: Should AZT vs d4T be used for initial ART ? (observational studies)
Settings: Multiple settings
Bibliography: 1. George C, Yesoda A, Jayakumar B, Lal L. A prospective study evaluating clinical outcomes and costs of three NNRTI-based HAART regimens in Kerala, India. *J Clin Pharm Ther* 2009;34:33-40. 2. Laurent C, Bourgeois A, Mpoudi-Ngolé E, Ciaffi L, Kouanfack C, Mougnutou R, Nkoué N, Calmy A, Koulla-Shiro S, Delaporte E. Tolerability and effectiveness of first-line regimens combining nevirapine and lamivudine plus zidovudine or stavudine in Cameroon. *AIDS Res Hum Retroviruses* 2008;24:393-9. 3. Mocroft A, Phillips AN, Ledergerber B, Katlama C, Chiesi A, Goebel FD, Knysz B, Antunes F, Reiss P, Lundgren JD. Relationship between antiretrovirals used as part of a cART regimen and CD4 cell count increases in patients with suppressed viremia. *AIDS* 2006;20:1141-50. 4. Njoroge J, Reidy W, John-Stewart G, Attwa M, Kiguru J, Ngumo R, Wambua N, Chung MH. *Incidence of peripheral neuropathy among patients receiving HAART regimens containing stavudine vs. zidovudine in Kenya* [Abstract TUPEB179]. 5th Conference on HIV Pathogenesis and Treatment and Prevention, Cape Town, South Africa, 19–22 July 2009. 5. Pazare AR, Khirsagar N, Gogatay N, Bajpai S. *Comparative study of incidence of hyperlactetemia/ lactic acidosis in stavudine vs. AZT based regime* [Abstract THPE0159]. XVII International AIDS Conference, Mexico City, Mexico, 3–8 August 2008.

Quality assessment							Summary of findings					Importance
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AZT	d4T	Relative (95% CI)	Absolute	Quality	
Mortality (observational)												
1	Observational studies	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	None	8/85 (9.4%)	11/84 (13.1%)	RR 0.72 (0.3 to 1.7)	37 fewer per 1000 (from 92 fewer to 92 more)	⊕⊕OO LOW	CRITICAL

Severe adverse events (observational)												
3	Observa-tional studies	No serious limitations	No serious inconsis-tency	No serious indirect-ness	No serious imprecision	None	14/415 (3.4%)	383/1941 (19.7%)	RR 0.42 (0.07 to 2.62)	114 fewer per 1000 (from 184 fewer to 320 more)	⊕⊕OO LOW	CRITICAL
Virological response (observational)												
1	Observa-tional studies	No serious limitations	No serious inconsis-tency	No serious indirect-ness	Serious[1]	None	33/85 (38.8%)	49/84 (58.3%)	RR 0.67 (0.48 to 0.92)	192 fewer per 1000 (from 47 fewer to 303 fewer)	⊕OOO VERY LOW	CRITICAL
Adherence/tolerability/retention (observational)												
2	Observa-tional studies	No serious limitations	No serious inconsis-tency	No serious indirect-ness	No serious imprecision	None	112/137 (81.8%)	108/135 (80%)	RR 1.02 (0.91 to 1.14)	16 more per 1000 (from 72 fewer to 112 more)	⊕⊕OO LOW	CRITICAL
Immunological response (observational) (Better indicated by higher values)												
2	Observa-tional studies	No serious limitations	No serious inconsis-tency	No serious indirect-ness	No serious imprecision	Reporting bias[2]	13123	7423	-	MD 16.4 lower (19.39 to 13.41 lower)	⊕OOO VERY LOW	IMPORTANT
Drug resistance (observational)												
1	Observa-tional studies	Serious[3]	No serious inconsis-tency	No serious indirect-ness	Serious[1]	None	4/85 (4.7%)	7/84 (8.3%)	RR 0.56 (0.17 to 1.86)	37 fewer per 1000 (from 69 fewer to 72 more)	⊕OOO VERY LOW	IMPORTANT

[1] Number of events <300 and/or confidence intervals include potential harm and benefit.

[2] 1 of 5 observational studies were industry-funded, although some were funded simultaneously by competitors.

[3] And 1 observational study (Laurent et al) reported on drug resistance, suggesting selective reporting.

Monitoring strategies for guiding when to switch

Authors: Larry William Chang, Jamal Harris
Date: 12 Aug 2009
Question: Should clinical monitoring vs immunological and clinical monitoring be used in guiding when to switch first-line antiretroviral therapy in adults in low-resource settings?
Settings: Low-resource settings
Bibliography: HBAC 2008, DART 2009

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other consideration	Clinical monitoring	Immunological and Clinical Monitoring	Relative (95% CI)	Absolute		
Mortality (follow-up median 3-5 years)												
2	Randomized ized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	?/2037[5]	?/2027[5]	HR 1.35 (1.12 to 1.63)	-	⊕⊕OO LOW	CRITICAL
AIDS-defining illness – not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
AIDS-defining illness or mortality (follow-up median 3-5 years)												
2	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None[4]	547/2037 (26.9%)[6]	414/2027 (20.4%)[6]	HR 1.33 (1.16 to 1.51)	58 more per 1000 (from 29 more to 88 more)	⊕⊕⊕O MODERATE	CRITICAL
Serious adverse event (follow-up median 5 years)												
1[7]	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	?/1660[8]	?/1656[8]	HR 1.12 (0.94 to 1.31)	-	⊕⊕OO LOW	CRITICAL

Unnecessary switch (switch to second-line therapy with undetectable viral load) (follow-up median 3 years)												
1[7]	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	15/377 (4%)	0/371 (0%)	RR 30.5 (1.83 to 508)	-	⊕⊕OO LOW	CRITICAL
Switch to second-line therapy (follow-up median 3–5 years)												
2	Randomized trials	Serious[1]	Serious[9]	No serious indirectness[2]	No serious imprecision	None[4]	331/2037 (16.2%)	365/2027 (18%)	RR 1.73 (0.37 to 8.06)	13 more per 100 (from 11 fewer to 127 more)	⊕⊕OO LOW	

[1] Unclear sequence generation and allocation concealment and blinding was not possible for both studies; lost to follow-up analyses not extensively presented for either trial but absolute numbers were relatively small.

[2] Patient populations preselected and within relatively well-resourced ART delivery programmes; however, as setting was low-resource, no downgrading occurred.

[3] Total number of events is small.

[4] Abstracts only, no peer-reviewed print publications of these data are available; however, as a significant amount of data was available from abstracts/conference presentations no downgrading occurred.

[5] Number with event not reported in either study. DART mortality in clinical arm 2.94/100 P-Y, in immunological + clinical arm 2.18/100 patients-year.

[6] In DART in clinical arm 6.94 events/100 patients-year, in immunological + clinical arm, 5.24 events/100 patients-year. In HBAC in clinical arm 7.57 events/100 patients-year in immunological + clinical arm 5.97 events/100 patients-year.

[7] DART study only.

[8] Number with event not reported.

[9] Number of events and point estimate varied widely between the two studies.

Authors: Larry William Chang, Jamal Harris
Date: 12 Aug 2009
Question: Should clinical monitoring vs virological, immunological, and clinical monitoring be used for guiding when to switch first-line antiretroviral therapy in adults in low-resource settings?
Settings: Low-resource settings
Bibliography: HBAC 2008

Quality assessment							Summary of findings					
							No of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical monitoring	Virological, immunological, and clinical monitoring	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	?/377[5]	?/368[5]	HR 1.58 (0.97 to 2.6)	-	⊕⊕OO LOW	CRITICAL
AIDS-defining illness – not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
AIDS-defining illness or mortality (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	72/377 (19.1%)[6]	47/368 (12.8%)[6]	HR 1.88 (1.25 to 2.84)	99 more per 1000 (from 29 more to 194 more)	⊕⊕OO LOW	CRITICAL
Unnecessary switch (switch to second-line therapy with undetectable viral load) (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	15/377 (4%)	0/368 (0%)	RR 30.3 (1.82 to 504)	-	⊕⊕OO LOW	CRITICAL

Virological treatment failure (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	19/377 (5%)	16/368 (4.3%)	RR 1.16 (0.6 to 2.19)	7 more per 1000 (from 17 fewer to 52 more)	⊕⊕OO LOW	IMPORTANT
Switch to second-line therapy (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	17/377 (4.5%)	7/368 (1.9%)	RR 2.37 (0.99 to 5.65)	26 more per 1000 (from 0 fewer to 88 more)	⊕⊕OO LOW	

[1] Unclear sequence generation and allocation concealment, lostto follow-up analyses not extensively presented but absolute numbers were relatively small, and blinding was not possible.

[2] Patient populations preselected and within relatively well-resourced ART delivery programmes; however, as this study was in a low-resource setting it was not downgraded.

[3] Total number of events was small.

[4] Abstracts only, no peer-reviewed print publications of these data are available; however, as a significant amount of data was available from abstracts/ conference presentations no downgrading occurred.

[5] Number with event not reported.

[6] In clinical arm 7.57 events/100 patients-year, in virological + immunological + clinical arm 4.80 events/100 patients-year.

Authors: Larry William Chang, Jamal Harris
Date: 12 Aug 2009
Question: Should clinical and immunological monitoring vs virological, immunological and clinical monitoring be used in guiding when to switch first-line antiretroviral therapy in adults in low-resource settings?
Settings: Low-resource settings.
Bibliography: H.B.A.C. 2008

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical and immunological monitoring	Virological, immunological and clinical monitoring	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	?/371[5]	?/368[5]	HR 1.14 (0.7 to 1.9)	-	⊕⊕OO LOW	CRITICAL
AIDS-defining illness – not reported												
0	-	-	-	-	-	-	-	-	-	-		CRITICAL
AIDS-defining illness or mortality (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	58/371 (15.6%)[6]	47/368 (12.8%)	HR 1.28 (0.84 to 1.97)	33 more per 1000 (from 19 fewer to 108 more)	⊕⊕OO LOW	CRITICAL
Unncessary switch (switch to second-line therapy with undetectable viral load) (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Very serious[7]	None[4]	0/371 (0%)	0/368 (0%)	Not estimable	-	⊕OOO VERY LOW	CRITICAL

Virological treatment failure (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	26/371 (7%)	16/368 (4.3%)	RR 1.61 (0.88 to 2.95)	27 more per 1000 (from 5 fewer to 85 more)	⊕⊕OO LOW	IMPORTANT
Switch to second-line therapy (follow-up median 3 years)												
1	Randomized trials	Serious[1]	No serious inconsistency	No serious indirectness[2]	Serious[3]	None[4]	4/371 (1.1%)	7/368 (1.9%)	RR 0.57 (0.17 to 1.92)	8 fewer per 1000 (from 16 fewer to 18 more)	⊕⊕OO LOW	

[1] Unclear sequence generation and allocation concealment, lost to follow-up analyses not extensively presented but absolute numbers were relatively small, and blinding was not possible.

[2] Patient populations preselected and within relatively well-resourced ART delivery programmes; however, as this study was in a low-resource setting it was not downgraded.

[3] Total number of events is small.

[4] Abstracts only, no peer-reviewed print publications of these data are available; however, as a significant amount of data was available from abstracts/conference presentations no downgrading occurred.

[5] Number with event not reported.

[6] In clinical + immunological arm 5.97 events/100 patients-year, in virological + immunological + clinical arm 4.80 events/100 patients-year.

7 Total number of events is very small.

Authors: Larry William Chang, Jamal Harris
Date: 14 Sep 2009
Question: Should virological, immunological, and clinical monitoring vs immunological and clinical monitoring be used in guiding when to switch first-line antiretroviral therapy in adults in low-resource settings?
Settings: Low-resource settings.
Bibliography: ARTLINC 2006, 2008

Quality assessment							Summary of findings					
							No of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Virological, immunological and clinical monitoring	Immunological and clinical monitoring	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up 12 months)												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	See comment[2]	See comment[2]	HR 2.28 (0.76 to 6.79)	-	⊕OOO VERY LOW	CRITICAL
Rate of switching												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	236/6369 (3.7%)	340/13744 (2.5%)	RR 1.60 (1.35 to 1.89)[4]	15 more per 1000 (from 9 more to 22 more)	⊕OOO VERY LOW	
Time to switch (7-18 months)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?/6369[5]	?/13744[5]	HR 1.38 (0.97 to 1.98)	-	⊕OOO VERY LOW	
Time to switch (19-30 months)												
1	Observational studies	Serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	?/2701[5]	?/6488[5]	HR 0.97 (0.58 to 1.6)	-	⊕OOO VERY LOW	

Time to switch (31-42 months)												
1	Observ-ational studies	Serious[3]	No serious inconsis-tency	No serious indirect-ness	No serious imprecision	None	?/923[5]	?/2802[5]	HR 0.29 (0.11 to 0.79)	-	⊕OOO VERY LOW	
CD4 cell count at time of switch												
1	Observ-ational studies	Serious[3]	No serious inconsis-tency	No serious indirect-ness	No serious imprecision	None	141 patients	261 patients	See com-ment.[6]	-	⊕OOO VERY LOW	

1 This outcome was a subgroup analysis, selection of non-exposed cohorts were not drawn from same communities as the exposed cohorts.

2 Number with event and at risk not reported.

3 Selection of non-exposed cohorts was not drawn from the same communities as the exposed cohorts; incomplete follow-up data on many participants.

4 Programmes with virological monitoring rate of switching was 3.2/100 patients-year (95% CI 2.2−2.6) versus 2.0/100 patients-year (95% CI 1.9−2.3) in those without ($p<0.0001$); RR here is a rate ratio.

5 Number with event not reported.

6 Programmes with virological monitoring CD4 cell count at time of switching was 161 cells/μl compared to 102 cells/μl in those without ($p=0.001$).

What to use in second-line

Authors: Humphreys E and Harris J
Date: 21 Aug 2009
Question: Should lamivudine (3TC) be maintained in second-line antiretroviral regimens for patients failing first-line therapy?
Bibliography: Fox Z, Dragsted U, Gerstoft J, et al. A randomized trial to evaluate continuation versus discontinuation of lamivudine in individuals failing a lamivudine-containing regimen: the COLATE trial. *Antiviral therapy* 2006;11(6):761-770.

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Maintaining 3TC in 2nd line	No 3TC in 2nd line (control)	Relative (95% CI)	Absolute		
Mortality – not measured[1]												
0	-	-	-	-	-				-	-		CRITICAL
Progression of disease – not measured												
0	-	-	-	-	-				-	-		CRITICAL
Severe adverse events (follow-up 48 weeks)												
1	Randomized trials	No serious limitations[3]	No serious inconsistency	Serious[4]	Serious[5]	None	-	-		Not estimable[2]	⊕⊕OO LOW	CRITICAL
Adherence/tolerability/retention – not reported												
0	-	-	-	-	-				-	-		CRITICAL
Virological response (follow-up 48 weeks; measured as: mean reduction from baseline log10 copies/ml of HIV RNA; better indicated by higher values)												
1	Randomized trials	No serious limitations	No serious inconsistency	Serious[4]	Serious[5]	None	28[6]	27	-	MD 0.4 lower (0.87 lower to 0.07 higher)	⊕⊕OO LOW	IMPORTANT

Proportion achieving VL <50 copies/ml (follow-up 48 weeks)												
1	Randomized trials	No serious limitations[2]	No serious inconsistency	Serious[4]	Serious[5]	None	38/65 (58.5%)	30/66 (45.5%)	RR 1.29 (0.92 to 1.80)	132 more per 1000 (from 36 fewer to 364 more)	⊕⊕OO LOW	IMPORTANT
Immunological response (follow-up 48 weeks; measured as: median increase in CD4 from baseline[7]; Better indicated by higher values)												
1	Randomized trials	No serious limitations	No serious inconsistency	Serious[4]	Serious[5]	None	65	66	-	Median increase 11	⊕⊕OO LOW	IMPORTANT

[1] Table 1 reports 1 death in Off3TC arm among patients who initiated treatment but discontinued.

[2] Numbers provided are non-fatal clinical adverse events per arm / total adverse events (among 49 participants). Further information not provided. No difference in adverse events between arms; 43/94 (45.7%) events in On3TC arm and 51/94 (54.3%) events in Off3TC arm (p=0.25).

[3] Open-label study; not downgraded for this. Partial funding from Industry in early phases of trial, also not downgraded for this (low risk of bias since study drug not favoured significantly by results).

[4] Clinician-optimized regimen; patients not from resource-limited setting (study population from 12 European countries).

[5] Few events or low number of patients.

[6] Numbers represent stratum A, an a priori subgroup of patients with only 1 prior 3TC-containing regimen (n=55). Similar results for stratum B, those with more than 1 prior regimen (n=76). The mean reductions from baseline in HIV RNA in overall groups were 1.4 log10 copies/ml (95% CI 1.1–1.6) in On3TC group and 1.5 (95% CI 1.2–1.7) in Off3TC group.

[7] No SD or 95% CI available from study (IQR provided); unable to report mean difference between groups although median difference reported as not significant (+87 in On3TC compared to 76 in Off3TC group, p=0.41).

Question: Should PI monotherapy be used for patients failing first-line therapy?

Bibliography: Arribas 2005; Arribas 2009a; Arribas 2009b; Cameron 2008; Delfraissy 2008; Guttmann 2008; Katlama 2009; Nunes 2007; Singh 2007; Waters 2008.

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	PI monotherapy	cART	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up 96 weeks)												
2	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	Serious[3]	None[4]	3/207 (1.4%)	1/153 (0.7%)	RR 1.46 (0.22 to 9.8)	3 more per 1000 (from 5 fewer to 58 more)	⊕⊕OO LOW	CRITICAL
Clinical disease progression – not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Serious adverse events (grade 3 or 4 adverse event; follow-up 1 study 24 weeks, 4 studies 48 weeks, 2 studies 96 weeks)[5]												
7	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	25/499 (5%)	26/472 (5.5%)	RR 1.02 (0.5 to 2.07)	1 more per 1000 (from 28 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Adherence/tolerability/retention (proportion on randomized treatment at study end; follow-up 1 study 24 weeks, 4 studies at 48 weeks, 3 studies at 96 weeks)												
8	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	506/607 (83.4%)	448/529 (84.7%)	RR 0.99 (0.95 to 1.04)	8 fewer per 1000 (from 42 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
Virological response (proportion with HIV RNA <50 copies/ml or lowest reported value; follow-up 6 studies 48 weeks, 3 studies 96 weeks)												
9	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	470/636 (73.9%)	460/560 (82.1%)	RR 0.94 (0.89 to 0.99)	49 fewer per 1000 (from 8 fewer to 90 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

Immunological response (measured with: mean increase from baseline CD4; better indicated by higher values; follow-up 1 study 24 weeks, 2 studies 48 weeks, 2 studies 96 weeks)												
5	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	338	256	-	Not pooled[6]	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (acquisition of major protease mutations; follow-up 4 studies 96 weeks, 2 studies 96 weeks)												
6	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	Serious[3]	None	10/551 (1.8%)	4/470 (0.9%)	RR 1.55 (0.48 to 5.01)	5 more per 1000 (from 4 fewer to 34 more)	⊕⊕OO LOW	IMPORTANT

[1] Open-label studies, not downgraded for this except for severe adverse events, which may be more prone to bias in open-label trials. Six of 9 studies industry-sponsored and 3 with unclear reporting of sponsorship.

[2] All but 2 studies (Cameron 2008 and Delfraissy 2008) were monotherapy studies that enrolled patients with viral suppression and/or who were ART-naive; indirect comparison to population who would use active PI in second-line after failure on first-line regimen.

[3] Low number of events (<300) and CI indicates potential for appreciable benefit and harm.

[4] Some concern for lack of clear mortality outcome reporting in the rest of the body of evidence since only 2 studies report deaths. Deaths reported in Cameron 2008 and Arribas 2009a were unrelated to study drugs; other studies presumed not to have any deaths (and mortality not primary end-point in any of the studies).

[5] ITT-E population used (randomized and dosed). Some variability in reporting; "serious adverse events" or "adverse events leading to discontinuation" used. Cameron 2008 not included as report states "3 patients discontinued due to adverse events" but does not specify which arm.

[6] Estimate not pooled because of variability (median vs. mean) in reporting, or lack of raw numbers. All studies report nonsignificant differences between arms in immunological changes.

Question: Should atazanavir/ritonavir vs. lopinavir/ritonavir be used for patients failing first-line therapy?

Bibliography: Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lance*t 2008;372:646-55. Molina JM, Andrade-Villanueva J, Echevarria J, et al. *Atazanavir/ritonavir vs. lopinavir/ritonavir in antiretroviral naive HIV-1-infected patients: CASTLE 96-week efficacy and safety.* 48^{tth} Annual ICAAC/IDSA Meeting, October 25–28, 2008, Washington DC. Abstract H-1250d.

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Atazanavir/ritonavir	Lopinavir / ritonavir	Relative (95% CI)	Absolute		
Mortality (follow-up 48 weeks)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	6/440 (1.4%)	6/443 (1.4%)	RR 1.01 (0.33 to 3.1)	0 more per 1000 (from 9 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up 96 weeks)[4]												
1	Randomized trials	Serious[1]	No serious inconsistency	Serious indirectness[2]	Serious[3]	None	63/441 (14.3%)	50/437 (11.4%)	RR 1.25 (0.88 to 1.77)	29 more per 1000 (from 14 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL
Clinical disease progression – not reported												
0	-	-	-	-	-				-	-		CRITICAL
Adherence/tolerability/retention (follow-up 48 weeks; adherence questionnaire)												
1	Randomized trials	Serious[1]	No serious inconsistency	Serious indirectness[2]	No serious imprecision	None	330/440 (75%)	316/443 (71.3%)	RR 1.05 (0.97 to 1.14)	36 more per 1000 (from 21 fewer to 100 more)	⊕⊕OO LOW	CRITICAL

Virological response, proportion <50 copies (follow-up 96 weeks)												
1	Random-ized trials	No serious limitations[1]	No serious inconsis-tency	Serious indirect-ness[2]	No serious imprecision	None	308/440 (70%)	279/443 (63%)	RR 1.08 (0.99 to 1.18)[5]	54 more per 1000 (from 7 fewer to 121 more)	⊕⊕⊕O MODER-ATE	IMPORTANT
Immunological response (follow-up mean 96 weeks; better indicated by higher values)												
1	Random-ized trials	No serious limitations[1]	No serious inconsis-tency	Serious indirect-ness[2]	No serious imprecision	None	440	443	-	MD 21.2 lower (43.3 lower to 0.9 higher)[6]	⊕⊕⊕O MODER-ATE	IMPORTANT
Drug resistance (follow-up 96 weeks) reported as major PI mutation												
1	Random-ized trials	No serious limitations[1]	No serious inconsis-tency	Serious indirect-ness[2]	Serious[3]	None	1/440 (2.3%)	0/443 (1.8%)	RR 1.26 (0.5 to 3.16)	5 more per 1000 (from 9 fewer to 39 more)	⊕⊕OO LOW	IMPORTANT

[1] Open-label study, sponsored by industry. Not downgraded for being open-label unless outcome is "severe adverse events" or "adherence" where non-blinded treatment could bias outcome.

[2] Study evaluates ART-naive population, which is indirect population from PI-naive patients who would use PI in second-line therapy after failure on NNRTI-based regimen.

[3] Low number of events, <300 and CI indicates potential for appreciable benefit and harm.

[4] Reported as, "serious adverse events". Of note, even subjects discontinued because of diarrhoea in LPV/r arm and 3 subjects discontinued because of jaundice/hyperbilirubinaemia in ATV/r arm.

[5] ITT analysis where non-completer or rebound=failure (TLOVR). At 48 week outcomes, numbers for TLOVR and confirmed virological response (CVR) were similar: for ATV/r 343/440 and LPV/r 338/443 (CVR) compared to ATV/r 343/440 and LPV/r 337/443 (TOLVR). CVR classifies rebounders who are resuppressed as responders. TLOVR classifies response as 2 measurements: <50 copies/ml and maintained (without discontinuation or rebound).

[6] Mean increase from baseline of CD4 cell count similar between groups: 268 cells/μl in ATV/r versus 290 cells/μl in LPV/r group at 96 weeks.

Question: Should darunavir/ritonavir vs. lopinavir/ritonavir be used for patients failing first-line therapy?
Settings:
Bibliography: Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96 week analysis. *AIDS* 2009;23:1679-88.

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Darunavir/ritonavir	Lopinavir/ritonavir	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up 96 weeks)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious indirectness[3]	Serious[2]	None	1/343 (0.3%)	5/346 (1.4%)	RR 0.2 (0.02 to 1.72)	12 fewer per 1000 (from 14 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up 96 weeks)[4]												
1	Randomized trials	Serious[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision	None	34/343 (9.9%)	55/346 (15.9%)	RR 0.62 (0.42 to 0.93)	60 fewer per 1000 (from 11 fewer to 92 fewer)	⊕⊕OO LOW	CRITICAL
Clinical disease progression – not reported												
0	-	-	-	-	-				-	-		CRITICAL
Adherence/tolerability/retention (follow-up 96 weeks; reported as retention, number still on randomized study drug[5])												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision	None	284/343 (82.8%)	265/346 (76.6%)	RR 1.08 (1 to 1.17)	61 more per 1000 (from 0 more to 130 more)	⊕⊕⊕O MODERATE	IMPORTANT

Virological response, proportion HIV-1 RNA <50 copies/ml (follow-up 96 weeks)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision	None	271/343 (79%)	246/346 (71.1%)	RR 1.11 (1.02 to 1.21)	78 more per 1000 (from 14 more to 149 more)	⊕⊕⊕O MODERATE	IMPORTANT
Immunological response (follow-up 96 weeks; better indicated by higher values)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious indirectness[3]	No serious imprecision	None	343	346	-	Not estimable[6]	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up 96 weeks), reported as acquired major PI mutation												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious indirectness[3]	Serious[2]	None	0/343 (0%)	0/346 (0%)	-	Not estimable[7]	⊕⊕OO LOW	IMPORTANT

[1] Open-label, industry-sponsored study. Downgraded for being open-label study for outcome of severe adverse events but not others.

[2] Low number of events <300 and CI indicates potential for benefit and harm.

[3] Evaluation in treatment-naive patients is an indirect measure of PI-naive patients who would use boosted PI in second-line therapy after failure of NNRTI-based regimen.

[4] Reported as "Any serious AE". For "Any AE leading to withdrawal," there were19/343 in DRV/r arm and 35/346 in LPV/r arm.

[5] In post hoc analysis by self-reported adherence, those adherent (>95% adherence) had similar VL response (<50 copies/ml) rates in both arms (82 and 78% in DRV/r and LPV/r, respectively). For those suboptimally adherent (<95%), VL response 76% in DRV/r arm compared to 53% in LPV/r arm ($p<0.0001$).

[6] Median change from baseline in CD4 cell count was 188 cells/μl in LPV/r group and 171 cells/μl in DRV/r group.

[7] No major PI mutations were found among those with VL >50 copies/ml who had baseline and end-point genotypes.

Question: Should fos-amprenavir/ritonavir vs. lopinavir/ritonavir be used for patients failing first-line therapy?
Settings:
Bibliography: Eron J, Yeni P, Gathe J et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet* 2006;368:476-82.

Quality assessment							Summary of findings					
							No. of patients		Effect			
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Fosamprenavir / ritonavir	Lopinavir / ritonavir	Relative (95% CI)	Absolute	Quality	Importance
Mortality (follow-up median 48 weeks)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	Serious[3]	None	4/443 (0.9%)	1/444 (0.2%)	RR 4.01 (0.45 to 35.73)	7 more per 1000 (from 1 fewer to 78 more)	⊕⊕OO LOW	CRITICAL
Severe adverse events (follow-up median 48 weeks; adverse events leading to discontinuation)												
1	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	53/436 (12.2%)	43/443 (9.7%)	RR 1.25 (0.86 to 1.83)	24 more per 1000 (from 14 fewer to 81 more)	⊕OOO VERY LOW	CRITICAL
Clinical disease progression or death (follow-up median 48 weeks)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	Serious[3]	None	11/443 (2.5%)	11/444 (2.5%)	RR 1 (0.44 to 2.29)	0 fewer per 1000 (from 14 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
Adherence/tolerability/retention (follow-up median 48 weeks; adherence by pill counts reported as median percentage)												
1	Randomized trials	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	427/443 (96.4%)	435/444 (98%)	RR 0.98 (0.96 to 1.01)	20 fewer per 1000 (from 39 fewer to 10 more)	⊕⊕OO LOW	CRITICAL

Immunological response (follow-up median 48 weeks; measured with: median increase in CD4 count from baseline; better indicated by higher values)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	443	444	-	Not estimable[4]	⊕⊕⊕O MODERATE	IMPORTANT
Virological response, proportion <50 copies/ml (follow-up median 48 weeks)												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	285/443 (64.3%)	288/444 (64.9%)	RR 0.99 (0.9 to 1.09)	6 fewer per 1000 (from 65 fewer to 58 more)	⊕⊕⊕O MODERATE	IMPORTANT
Drug resistance (follow-up median 48 weeks), reported as acquired major PI mutations												
1	Randomized trials	No serious limitations[1]	No serious inconsistency	Serious[2]	Serious[3]	None	0/443 (0%)	0/444 (0%)	-	Not estimable[5]	⊕⊕OO LOW	IMPORTANT

[1] Open-label study; sponsored by industry. Not downgraded for this other than for severe adverse events and adherence, which may be subject to bias in open-label study.

[2] Evaluates comparison in ART-naive population, which is indirect to PI-naive populations starting PI-based second-line therapy after NNRTI first-line.

[3] Low number of events <300 and CI indicates potential for appreciable benefit and harm.

[4] Median increase in CD4 from baseline 176 cells/μl (IQR 106-281) in FPV/r group and 191 cells/μl (IQR 124-287) in LPV/r group

[5] No major PI associated mutations in either arm among the 35 patients who had protocol-defined failure and baseline and end-point genotypes available.

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