

# RAPID ADVICE

Antiretroviral therapy for HIV infection in adults and adolescents

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Antiretroviral therapy for HIV infection in adults and adolescents

### **Abbreviations**

3TC lamivudine ABC abacavir

ART antiretroviral therapy
ARV antiretroviral (drug)

ATV atazanavir

AZT zidovudine (also known as ZDV) bPI boosted protease inhibitor

CD4 T-lymphocyte bearing CD4+ receptor
CDC Centers for Disease Control and Prevention

CIPRA HT001 Comprehensive International Program of Research on AIDS in Haiti (clinical trial)

DART Development of Antiretroviral Therapy in Africa (clinical trial)

d4T stavudine
ddl didanosine
EFV efavirenz
FBC full blood count

FDC fixed-dose combination

FTC emtricitabine

GRADE Grading of Recommendations, Assessment, Development and Evaluation

HBAC Home Based AIDS Care (clinical trial)
HIV human immunodeficiency virus

HBV hepatitis B virus

IAS International AIDS Society

IRIS immune reconstitution inflammatory syndrome

LPV lopinavir

NNRTI non-nucleoside reverse transcriptase inhibitor NRTI nucleoside reverse transcriptase inhibitor

NVP nevirapine

PEPFAR US President's Plan for Emergency AIDS Relief

PI protease inhibitor

PMTCT prevention of mother-to-child transmission

PLHIV people living with HIV
/r low-dose ritonavir
RCT randomized clinical trial
RTI reverse transcriptase inhibitor

RTV ritonavir

SAPIT Starting Antiretroviral Therapy at Three Points In Tuberculosis Therapy (clinical trial)

TB tuberculosis

TDF tenofovir disoproxil fumarate

VL viral load

UNAIDS Joint United Nations Programme on HIV/AIDS

WHO World Health Organization

# Contents

Abbreviations		2
1.	Overview	4
1.1	Background	4
1.2	Why a revision?	4
1.3	Guiding principles	4
2.	The revision process	5
2.1	Retrieving, summarizing and presenting the evidence	5
2.2	Consensus, external review and updating	5
3.	Guideline timing and publication	6
4.	Dissemination, adaptation, implementation and evaluation	7
5.	Declarations of interest	8
6.	Collaboration with external partners	9
7.	Key recommendations	10
8.	References	15
9.	Annex 1	17

### 1. Overview

#### 1.1 Background

The guideline Antiretroviral therapy for hiv infection in adults and adolescents, developed by World Health Organization (WHO), was first published in 2002, simplified in 2003 and was updated in 2006. The guideline continues to follow the principles of a public health approach, aiming to optimize outcomes, including the quality of life and survival, of people living with HIV (PLHIV), and to act as a reference tool for countries to adopt and adapt according to their national circumstances.

During 2009, WHO has worked to update the guideline through a series of coordinated efforts to review and synthesize emerging evidence on when to initiate antiretroviral therapy (ART), what drug regimens to use, and the management of co-infections and treatment failure. This evidence has been assembled following systematic reviews, GRADE' profile preparation and analysis, consultations with PLHIV, cost and economic impact studies, country-level feasibility assessment, and comparisons of current country guidelines.

The groups who developed this revised guideline were: an internal WHO ART Guideline Working Group (convened in April 2009), the ART Guideline Drafting Group (convened in September 2009), the external ART Peer Review Panel (convened in September 2009), and the full ART Guideline Review Committee (convened in October 2009). The members are listed in Annex 1.

#### 1.2 Why a revision?

Since the last guideline revision in 2006, new and compelling evidence has become available, particularly concerning the earlier start of ART. There is increasing evidence of improved survival and reduced HIV-related illnesses with the earlier initiation of antiretroviral therapy. Studies support that improved access to ART has a significant impact on the prevention of HIV transmission. Stavudine (d4T) continues to play a critical role in the scaling-up of ART in low- and middle-income countries; however, its cumulative toxicity is unacceptable to PLHIV and to many health care providers. Newer, more patient friendly but currently more expensive ART regimens are available.

The aim of the guideline is to outline standards for high quality care of PLHIV, by providing evidence-based recommendations, while considering the risks and benefits, acceptability, feasibility, cost and financial implications.

The target audience is primarily national treatment advisory groups.

The key recommendations contained herein are released as *Rapid advice* because several countries with the highest burden of HIV infection currently are in the process of changing their national guideline for HIV treatment and care, and updating estimates for 2010 Universal Access reporting. This *Rapid advice* focuses on two key areas of the full guideline; when to start ART and what ARVs to use in adults, adolescents, pregnant women, tuberculosis (TB) and hepatitis B (HBV) co-infection.

#### 1.3 Guiding principles

The ART Guideline Review Committee discussed and agreed upon a set of principles that should be used in developing national treatment recommendations. The principal consideration was that public health interventions should secure the greatest likelihood of survival and quality of life for the greatest numbers of PLHIV.

#### 1. Do no harm

When introducing changes preserve access for the sickest and most in need.

#### 2. Ensure access and equity

All clinically eligible people should be able to enter treatment services (including ART) with fair and equitable distribution of treatment services.

#### 3. Promote quality and efficiency

Ensure delivery of the highest standards of care within a public health approach so as to achieve the greatest health impact with the optimal use of available human and financial resources.

#### 4. Ensure sustainability

Understand the long-term consequences of change with the vision of providing continued, life-long access to ART for those in need.

In this context, the individual rights of PLHIV should not be forfeited in the course of a public health approach.

<sup>\*</sup> http://www.gradeworkinggroup.org/index.htm

### 2. The revision process

# 2.1 Retrieving, summarizing and presenting the evidence

The PICO" questions to be considered were agreed upon by the internal WHO ART Guideline Working Group in May 2009. A series of activities then were undertaken to prepare for the October 2009 guideline review meeting:

- 1. GRADE profiles were prepared for the key PICO questions:
  - i. when to start ART;
  - ii. what to use in first-line and second-line antiretroviral regimens;
  - iii. when to switch to a second-line regimen.
- Systematic reviews of the literature were conducted on ARV drug interactions with drugs for TB, hepatitis, malaria, and opioids; ART management for HIV/HBV co-infection; ART toxicity summaries for tenofovir, zidovudine, nevirapine and stavudine; the safety of efavirenz; the teratogenicity of efavirenz; a low-dose stavudine safety profile; and reviews of CD4 and viral load laboratory technologies.
- An impact assessment was conducted to estimate the number of PLHIV in need of treatment according to various proposed CD4 initiation thresholds.
- 4. Consultations were conducted with three organizations representing PLHIV and the findings summarized.
- 5. Costing information was prepared based on studies of procurement and production of ARVs.
- 6. A feasibility assessment was conducted for the introduction of the proposed guideline in Malawi (a similar assessment is ongoing in Tanzania).
- 7. A report was produced on issues related to adherence to ART for PLHIV, including adolescents.
- 8. A review was undertaken to study and compare current ART guidelines from 26 countries.
- ART failure criteria were reviewed using data from ART-LINC and other studies.

The GRADE evidence profiles, and the full set of supporting documentation will be included and or referenced in the guideline."

#### 2.2 Consensus, external review and updating

Existing recommendations were reviewed and revised at the September 2009 meeting of the ART Guideline Drafting Group. Based on presentations and individual review of the available evidence described above, the group compiled risk-benefit analysis for each area of interest. A table that includes the following domains: existing recommendations; new recommendations; quality and grade of evidence for the critical outcomes (mortality, disease progression and serious adverse events); benefits; risks; values; acceptability; costs; feasibility; gaps and research needs was prepared for each set of recommendations. Disagreements were debated during plenary and group sessions and consensus sought.

The ART Peer Review Panel reviewed and revised the risk-benefit tables and draft recommendations prepared by the ART Guideline Drafting Group and responded with their comments and other input via the ART Guidelines 2009 page of WHO's EZCollab website. Reviewers debated and exchanged ideas within EZCollab and during teleconferences. Their suggestions and comments were collated and posted on the EZCollab website. The revised recommendations were presented to the ART Guideline Review Committee in October 2009.

At the October 2009 ART Guideline Review Meeting, each subject area was reviewed, discussed and consensus sought on each recommendation and the ranking of each recommendation.

The full guideline document will be reviewed again by 2012.

 $<sup>^{\</sup>star\star}$  PICO is an acronym that describes the elements of a well-formed clinical question. The structure includes: 'P' for the patient or population; 'l' for the intervention of interest; 'C' for comparison; and 'O' for outcome

 $<sup>^{\</sup>star\star\star}$  The full set of background materials can be requested by emailing hiv-aids@ who.int.

# 3. Guideline timing and publication

This Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents will be published online. Given the short life-span of the Rapid Advice, it will be posted online in English. However, requests from WHO Regional Offices for translation into other languages will be supported from WHO Headquarters.

It is expected that a draft of the full guideline will be available in February 2010 for final clearance, with publication and dissemination anticipated to start in March or April 2010.

### 4. Dissemination, adaptation, implementation and evaluation

WHO is working closely with WHO Regional and Country Offices, UN and other implementing partners to plan for rapid dissemination, adaptation and implementation of the new recommendations. Much experience has been obtained from previous ART guidelines, and active support for guideline revision at country level is needed. Key steps in the dissemination include:

- Release of the *Rapid advice*
- Production and publication of the full guideline, with translation into other languages
- Rapid development of adaptation and transition tools
- Briefings and joint planning for dissemination with international and national implementing partners
- Regional conferences and workshops, to support country adaptation

Adaptation and transition tools are designed to:

- Assist countries prioritize limited resources to facilitate full implementation over time
- Not compromise ART access or exclude those most in need
- Not disrupt existing scale up efforts or threaten adherence
- Move progressively towards adopting all recommendations

The WHO and UNAIDS are finalizing the global and country tools required for estimations of treatment and resource needs, in time for 2010 universal access reporting.

### 5. Declarations of interest

Forms were collected from every member of each group. Two declarations were made and were determined not to constitute conflicts of interest by the core guideline team. The ART Peer Review Panel was advised via the WHO's EZCollab website of a member's declaration of potential conflict (P. Cahn) and the ART Peer Review Panel concluded that there was no conflict of interest. The declaration of potential conflict of a member of the ART Guideline Review Committee (C. Holmes) was discussed with the assembled ART Guideline Review Committee at the October 2009 meeting. The ART Guideline Review Committee concluded that there was no conflict of interest.

# 6. Collaboration with external partners

There are no external collaborators specific to this *Rapid advice*. However, several partners have been engaged in the development of the guideline. All collaborations will be detailed in the full guideline.

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.

### 7. Key recommendations

#### **RECOMMENDATION 1**

#### When to start

 Start antiretroviral treatment in all patients with HIV who have CD4 count ≤350 cells/mm³ irrespective of clinical symptoms

(Strong recommendation, moderate quality of evidence)

CD4 testing is required to identify if patients with HIV and WHO clinical stage 1 or 2 disease need to start antiretroviral treatment.

(Strong recommendation, low quality of evidence)

3. Start antiretroviral treatment in all patients with HIV and WHO clinical stage 3 or 4 irrespective of CD4 count. (Strong recommendation, low quality of evidence)

**Remarks**: In developing these recommendations, the panel placed high value on avoiding death, disease progression and HIV transmission over and above cost and feasibility. The recommendations are supported by moderate quality of evidence for critical patient and public health outcomes from one RCT, the CIPRA-HT001 (a singlecentre trial in Haiti) and one post hoc analysis nested in a RCT, the SMART trial (a multicentre study in 33 predominantly high income countries).<sup>1, 2</sup> In the GRADE profile, pooled data from these two studies provide moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/mm³ reduces mortality rates in asymptomatic, ART-naive, HIV-infected people. The panel also reviewed large observational data sets from both resource limited and high resource settings which are consistent with data from the RCTs but these did not add to the overall quality of the evidence.<sup>3-6</sup> The panel considered that starting ART earlier is 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.

Considering the uncertain prognostic value of some WHO clinical stage 2 conditions and recent modelling and observational data suggesting that more than 50% of HIV-infected patients with this clinical stage have a CD4 count of  $\leq$ 350 cells/mm³, the panel recommended HIV-infected individuals with WHO clinical stage 1 and 2 should have access to CD4 testing to decide if treatment should be initiated.

#### **RECOMMENDATION 2**

#### What to start

Start one of the following regimens in ART-naïve 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)

Remarks: In developing these recommendations the panel placed high value on avoiding the disfiguring, unpleasant and potentially life threatening toxicity of d4T, the need to select regimens suitable for use in most patient groups, and the benefits of using fixed dose combinations.

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

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- or TDF-based first-line regimens, based on an assessment of the cost and feasibility. Systems to prevent, monitor and manage d4T-related toxicities should be implemented.

It is recommended that programs select the preferred regimen(s) applicable to the majority of PLHIV. The introduction of safer but currently more expensive first-line ARTs needs to be phased-in 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.

WHO will develop tools to assist countries/programs in the transition to and implementation of these recommendations.

#### **RECOMMENDATION 3**

#### ART for HIV/tuberculosis co-infection

- Start ART in all HIV-infected individuals with active tuberculosis (TB) irrespective of CD4 cell count.
   (Strong recommendation, low quality of evidence)
- Start TB treatment first, followed by ART as soon as possible after starting TB treatment. (Strong recommendation, moderate quality of evidence)
- Use efavirenz (EFV) as the preferred non-nucleoside reverse transcriptase inhibitor (NNRTI) in patients starting ART while on TB treatment.

(Strong recommendation, high quality of evidence)

Remarks: In developing these recommendations, the panel placed high value on the reduction of early mortality from HIV/TB coinfection, the reduction of TB transmission when ART is initiated earlier in all individuals with TB and improved management of TB.

On the question of when to initiate ART in TB infection, one RCT (SAPIT trial) provides moderate evidence for early initiation of ART in terms of reduced all-cause mortality, improved TB outcomes and reduced incidence of immune reconstitution inflammatory syndrome (IRIS), but there are limited data on the need to initiate ART in patients with TB and CD4 >350 cells/mm³. <sup>7</sup>

On the question of the impact on TB transmission and incidence, ART has been reported to reduce TB rates by up to 90% at an individual level, by 60% at a population level and to reduce TB recurrence rates by 50%.<sup>8-10</sup> Modeling suggests that initiation of ART for all those with HIV/TB co-infection, if accompanied by high levels of coverage and ART adherence, reduces the number of TB cases, TB mortality rates and TB transmission at a population level.<sup>11</sup>

Further modeling suggests that starting ART less than five years after initial HIV infection could reduce the incidence of TB by 60% to 70%. (B Williams, submitted for publication)

On the question of which NNRTI to start, the recommendations in the 2006 ART guideline were maintained, specifically EFV is recommended because of less interaction with rifampicin compared to NVP.

# RECOMMENDATION 4 ART for HIV/HBV co-infection

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

**Remarks**: In developing these recommendations, the panel placed high value on promoting HBV diagnosis and more effective treatment of HIV/HBV co-infection.

The systematic review on this topic did not find RCTs which addressed critical HIV outcomes (death, disease progression, severe adverse events) and the GRADE profile reported only on outcomes related to HBV (HBV viral load and HBV drug resistance).

On the question of when to start ART in HIV/HBV co-infection, there are no trials comparing early versus late initiation of ART. However, observational data support that individuals with HIV/HBV co-infection have a 3- to 6-fold risk of developing chronic HBV, an increased risk of fibrosis and cirrhosis and a 17-fold increased risk of death compared to HBV-infected individuals without HIV infection. Similarly, observational data support a reduction in liver related disease with earlier and HBV-active combination ART.

On the question of what ART to start in HIV/HBV co-infection, there are data from one RCT supporting the use of at least two agents with activity against HBV in terms of improved HBV viral load response and reduced development of HBV drug resistance.<sup>12</sup>

#### **RECOMMENDATION 5**

#### ART for pregnant women

- Start ART in all pregnant women with HIV and CD4 count ≤350 cells/mm³, irrespective of clinical symptoms.
   (Strong recommendation, moderate quality of evidence)
- CD4 testing is required to identify if pregnant women with HIV and WHO clinical stage 1 or 2 disease need to start antiretroviral treatment or prophylaxis. (Strong recommendation, low quality of evidence)
- 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-naïve pregnant women eligible for treatment.

(Strong recommendation, moderate quality of evidence)

AZT + 3TC + EFV

AZT + 3TC + NVP

TDF + 3TC or FTC+ EFV

TDF + 3TC or FTC + NVP

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

Remarks: In developing these recommendations, the ART and PMTCT panels placed high value on ensuring treatment is started early for pregnant women with HIV to avoid mother-to-child transmission and improve maternal and child-health outcomes, over and above concerns for the cost or feasibility.

On the question of when to start, no studies specific to pregnant women were identified. Overall evidence supports strong recommendations for the reduction of mortality, disease progression, severe adverse events, the risk of TB and the risk of HIV transmission (sexual and vertical). As with the recommendation on when to start in the general population, the panel recognised the uncertainty around the prognostic value of some WHO clinical stage 2 conditions and data from modelling and observational studies indicate that more than 50% of HIV-infected patients with this clinical stage have a CD4 count of  $\leq$ 350 cells/mm³. Therefore, the panel recommended all pregnant women with WHO clinical stages 1 and 2 have access to CD4 testing to decide when to start treatment.

On the question of **what to start**, no GRADE profiles were prepared as no RCTs were identified for the use of AZT+3TC+NVP specifically in pregnant women. Cohort studies report reduction of HIV

transmission and death.<sup>13</sup> There is no evidence to suggest an increase in maternal serious adverse events and no studies specifically evaluating maternal response to ART. Pregnancy 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.<sup>14</sup>

There is very low quality, conflicting evidence on the risks of EFV causing neural tube defects. The overall rates of birth defects reported in association with EFV, NVP, lopinavir/ritonavir (LPV/r) or TDF appear similar and are consistent with rates reported in congenital defects' registries from general populations. Since neural tube closure occurs in the first 28 days and very few pregnancies are recognised by this time, the actual risks from starting EFV based ART in the first trimester are difficult to estimate.

The review of NVP safety in pregnant women with CD4 count 250–350 cells/mm³ did not confirm an increased risk of serious adverse events and the panel concluded that the benefits of using NVP in this situation outweigh the risks of not initiating ART.

The panel was unable to conclude from the evidence reviewed whether there are benefits associated with the use of EFV vis a vis 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.

## **RECOMMENDATION 6**When to switch ART

- 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 above 5 000 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)

Remarks: In developing 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. They also valued the need to optimize the use of virological monitoring and ensure adherence.

Based on the pooled analysis of the size effects from two randomized trials (HBAC and DART trials), 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 no difference in serious adverse events. 15, 16 However, in one of these trials (HBAC trial), combined immunological and clinical monitoring was compared to combined virological, immunological, and clinical monitoring, and resulted in no difference in mortality, disease progression, unnecessary switches or virological treatment failures. 15

## **RECOMMENDATION 7**Second-line ART

- A boosted protease inhibitor (PI/r) 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 boosted PI's 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, use TDF + 3TC or FTC as the NRTI backbone in second-line.
  - If TDF has been used in first-line, use AZT + 3TC as the NRTI backbone in second-line.

(Strong recommendation, moderate quality of evidence)

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

On the question of whether PI monotherapy could be used as secondline ART, there is moderate quality of evidence from 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.<sup>17-22</sup> The panel concluded that an NRTI backbone should be maintained.

On the question of which bPI to use in second-line therapy, there is moderate quality of evidence that ATV/r is non-inferior to LPV/r (in combination with TDF and an optimized second NRTI) in treatment-experienced patients.<sup>23</sup> Non-serious adverse events varied by boosted PI with no significant difference in serious adverse events.

On the question of which NRTI backbone to use in second-line, few studies of relevance were identified. The recommended NRTI sequencing is based on likely resistance mutations and potential for retained antiviral activity. If AZT+3TC are used in first-line with sensitive monitoring and early switching, the NRTIs with remaining activity are TDF and ddl, (both very likely) and ABC (likely). In the scenario of insensitive monitoring and late switching, TDF and ddl activity are less likely, with activity of ABC unlikely. If TDF+3TC are use in first-line, with early switching, the NRTIs with remaining activity are AZT and d4T (very likely), ddl, ABC (possible). In the scenario of late switching, activity of AZT and d4T is very likely, with activity of ddl and ABC unlikely. Retained activity of 3TC is likely in the early switching scenario and less likely in the case of late switching. AZT+3TC, TDF+FTC and TDF+3TC are available as fixed-dose combinations.

#### **RECOMMENDATION 8**

#### Third-line regimens

- 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)
- 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)

Remarks: The panel were 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 whilst maintaining increased access to first-line therapy. It was recognized that many counties have financial constraints that might limit the adoption of third-line regimens.

From a targeted literature review of relevant studies, the evidence is limited with few studies of newer agents in resource-limited settings. Data from RCTs predominantly in developed countries are available for boosted darunavir, 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 impact the provision of first-line ART. There was also uncertainty about what third-line drugs should be provided and many studies are ongoing.

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### 9. Annex 1

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#### 2009 ART guideline review meeting

Hotel Ramada Encore, Geneva, 14-16 October 2009

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