2009 Recommendations for Antiretroviral Therapy in Adults and Adolescents

Summary of WHO Rapid Advice
December 2009
The Global Impact of ART Scale up

The number of AIDS-related deaths has declined by over 10% over the past five years...

Since 1996 the availability of effective treatment, has saved some 2.9 million lives...
Access to ART continues to expand rapidly...

As of end of 2008:
9.5 million people need ART
4 million are on ART in LMIC
1 million newly started ART in 2008

ART coverage in low- and middle-income countries, (adults ≥15 years to December 2008)

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Reported number of adults (≥15 years) receiving ARV therapy</th>
<th>Estimated number of adults needing ARV therapy</th>
<th>Antiretroviral therapy coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>2,700,000</td>
<td>6,100,000</td>
<td>44%</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>429,000</td>
<td>800,000</td>
<td>54%</td>
</tr>
<tr>
<td>East, South and South-East Asia</td>
<td>537,000</td>
<td>1,500,000</td>
<td>36%</td>
</tr>
<tr>
<td>Europe and Central Asia</td>
<td>80,000</td>
<td>370,000</td>
<td>22%</td>
</tr>
<tr>
<td>North Africa and the Middle East</td>
<td>9,400</td>
<td>62,000</td>
<td>15%</td>
</tr>
<tr>
<td>Total</td>
<td>3,755,000</td>
<td>8,800,000 [8.1–9.5 million]</td>
<td>43% [39–46%]</td>
</tr>
</tbody>
</table>

This represents a 36% increase in 2008 and a ten-fold increase over the last 5 years.
Major Ingredients for successful ART scale up

- Political commitment
- Specified population/geographical targets
- Generic fixed-dose combinations
- Public health approaches-standardised simplified clinical management protocols
- Task shifting/sharing

ART Scale up Progression in Resource Limited Settings (2003 - 2008)

- Cumulative Number of Patients Receiving ART
- Mean Rate of Increase (patients on ART/month)

<table>
<thead>
<tr>
<th>Month</th>
<th>Cumulative Number of Patients on ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec-03</td>
<td>500,000</td>
</tr>
<tr>
<td>Jun-04</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Dec-04</td>
<td>1,500,000</td>
</tr>
<tr>
<td>Jun-05</td>
<td>2,000,000</td>
</tr>
<tr>
<td>Dec-05</td>
<td>2,500,000</td>
</tr>
<tr>
<td>Jun-06</td>
<td>3,000,000</td>
</tr>
<tr>
<td>Dec-06</td>
<td>3,500,000</td>
</tr>
<tr>
<td>Jun-07</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Dec-07</td>
<td>4,500,000</td>
</tr>
<tr>
<td>Jun-08</td>
<td>5,000,000</td>
</tr>
</tbody>
</table>

Number of Patients on ART/Month

- Median # new starts on ART/month
  - South Africa 16,000
  - India 7,000
  - Thailand 1,200
The WHO ART guideline revision process

1/09 Scope the work
3/09 WHO guideline review committee approval
4/09 Identify guideline group (Chair, core group, peer review group)
5/09 Formulate questions, agree on relevant outcomes
6-7/09 Retrieve evidence, evaluate and synthesize
7/09 Prepare benefit/risk profiles, access cost implications, PLHIV consultations
9/09 Draft recommendations
10/09 Peer review - key opinion leaders and treatment working group
11/09 Approve final recommendations, guideline meeting
12/09 Online publication - Rapid advice
02/10 Print publication and dissemination - Final guidelines

Populations considered
- HIV+ adults and adolescents
- HIV+ pregnant women
- HIV+ with TB co-infection
- HIV+ with hepatitis B co-infection
- HIV+ with hepatitis C co-infection

Areas reviewed
- How to diagnose earlier
- How to monitor
- When to start
- What to use 1st line
- What to use 2nd line
- Third line?

Critical health outcomes considered
- Mortality
- Disease progression (morbidity)
- Severe or treatment limiting adverse events
- Adherence & retention on ART
- Durability of regimen effect
- Reduction of HIV transmission
- Cost
- CD4 response
- HIV viral load
- HIV drug resistance
- HBV viral load
- HBV drug resistance

WHO, 2009
A cohort of preparatory activities....

- Evidence profiles (systematic reviews)
- Feasibility assessment
- Costing Projections
- PLHIV consultations
- Assessment of country guidelines
- Drug safety profiles
- Drug-drug interaction profiles
- Peer and expert review consultations
- Cost-effectiveness assessment

2009 update
Quality of evidence using GRADE

The extent to which one can be confident that an estimate of effect or association is correct.

<table>
<thead>
<tr>
<th>Quality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Considerable confidence in estimate of effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research likely to have impact on confidence in estimate, may change estimate</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to impact on confidence, likely to change the estimate</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>
Strength of recommendation

The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

**Desirable effects**
- Individual & population health benefits
- Improved quality of life
- Cost efficiencies

**Undesirable effects**
- Adverse outcomes
- Decreased quality of life
- Increasing health costs
Four guiding principles...

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
Four key messages...

1) **Start ART earlier**
   
   Use ART before becoming sick starting when CD4 threshold is less than 350 cells/mm³

2) **Use less toxic and more patient-friendly options**
   
   Reduce the risk of adverse events and improve adherence by using less toxic drugs as fixed dose combinations

3) **Improve management of TB/HIV and HBV/HIV co infections**
   
   Start ART in all PLHIV who have active TB and chronic active hepatitis B disease irrespective of CD4 cell count.

4) **Promote strategic use of laboratory monitoring**
   
   Use laboratory monitoring such as CD4 and viral load to improve efficiency and quality of HIV treatment and care
When to start

- Start antiretroviral treatment in all patients with HIV who have CD4 count \( \leq 350 \text{ cells/mm}^3 \) 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)*

- 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)*

*The panel placed high value on avoiding death, disease progression and likely HIV transmission over and above cost and feasibility*
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)*

The panel placed high value on avoiding d4T toxicity, the need to select regimens that are 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.
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)*

*The panel placed high value on reduction of early mortality from HIV/TB co-infection and reduction of TB transmission when ART is initiated earlier and improved management of TB*
**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)*

*The panel placed high value on promoting HBV diagnosis and more effective treatment of HIV/HBV co-infection*
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)*

- Start one the following regimens in ART-naïve pregnant women eligible for treatment:
  - AZT + 3TC + EFV
  - AZT + 3TC + NVP
  - TDF + 3TC/FTC+ EFV
  - TDF + 3TC/FTC + NVP
  
  *(Strong recommendation, moderate quality of evidence)*

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

The ART and PMCT panels placed high value on ensuring treatment is started early for pregnant women to avoid mother-to-child transmission and improve maternal and child-health outcomes, over and above concerns for the cost or feasibility
When to Switch ART

- Where available use viral load (VL) to confirm treatment failure
  (Strong recommendation, low quality of evidence)

- Where routinely available use VL every 6 months to detect viral replication
  (Conditional recommendation, low quality of evidence)

- A persistent viral load above 5,000 copies/ml confirms treatment failure
  (Conditional recommendation, low quality of evidence)

- Where VL is not available, use immunological criteria to confirm clinical failure
  (Strong recommendation, moderate quality of evidence)

The panel were concerned by the limitations of clinical/immunological monitoring for diagnosing treatment failure, and placed high value on avoiding premature switching to expensive second line ART, the need to optimize the use of virological monitoring and ensure adherence
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)*

- ATV/r and LPV/r are the preferred boosted PI's for second-line ART.
  
  *(Strong recommendation, moderate quality of evidence)*

- 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)*

*The panel placed high value on using simpler second-line regimens and the availability of heat-stable, fixed-dose combinations*
Third-line regimens

- National programs 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)*

- 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)*

The panel was concerned by the reports of high mortality for patients failing second-line therapy, but placed high value on balancing the need to develop policies for third-line therapy while maintaining increased access to first-line therapy. It was recognised that most counties have financial constrains that might limit the adoption of third-line regimens.
New ART Recommendations: Likely benefits

- Reduce death, disability and morbidity
- Reduce HIV and TB transmission
- Reduce costs for OI and cancer management
- Reduce orphan hood
- Improve maternal and child health outcomes
- Reduce toxicity
New ART Recommendations: Major implications & challenges

- ART coverage – will apparently decrease

- Treatment cost - will initially increase (but long term benefits justify this investment)

- Lab infrastructure - need for wider access to CD4 and VL, Hep B test

- Human resources – MCH, TB and harm reduction services all likely to face increased demands

- Potential to exacerbate waiting lists

- Prioritization (when to start vs. what to use)

- Global Fund and other grants – may need to be re-programmed

Phased introduction & transition is required, based on assessment of country capacity, need & resources
What is the impact of early ART therapy?

Preliminary estimates suggest that the provision of early therapy (<350 CD4+) and **high coverage (to 85%)** would produce:

- Increase the number of people in need (**50%**)
- Increase the financial requirements by **57%**
- Reduce deaths by **20%**
- Avert more than **1 million infections** between 2010 and 2015

![Graph showing the impact of early ART therapy](image-url)
Dissemination, adaptation & implementation

WHO will provide technical support & adaptation and transition tools to:

- Assist country guideline review process
- Move progressively towards adopting all recommendations
- Assist countries prioritize 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

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.
Currently, the median CD4 count at ART initiation is well below 200 in Africa and South/South-east Asia. Raising the eligibility criteria will not affect numbers on treatment unless potential patients are identified earlier and access to treatment expands.

**CD4 count at start of ART, 2003-2005**

42 countries, 176 sites, 33,008 patients

Numbers are median CD4 counts

*Source: Matthias Egger, Outcomes of Antiretroviral Treatment in Resource Limited and Industrialized Countries, CROI 2007.*
Mopping the floor while the tap is running

"For every two people put on treatment, five are newly infected."
Michel Sidibé (Executive Director, UNAIDS)