

## SUMMARY OF MAJOR RECOMMENDATIONS (2009 WHO ART Guidelines for Adults and Adolescents)

### When to start

#### Recommendations

1. Start antiretroviral treatment in all patients with HIV who have CD4 count  $\leq 350$  cells/mm<sup>3</sup> irrespective of clinical symptoms. **(Strong recommendation, moderate quality of evidence)**
2. 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)**

### Domains and considerations

#### Quality of evidence

Moderate quality of evidence supports strong recommendations for these clinical and immunological criteria for ART initiation for the critical outcomes of reduction in absolute risk of death, disease progression, including tuberculosis, occurrence of severe adverse events and the important outcome of HIV transmission (sexual and vertical routes).

One randomized clinical trial (RCT) specifically aimed to answer the PICO question: *When is the optimal time to initiate ART in asymptomatic, treatment-naïve, HIV-infected adults?* (CIPRA-HT001 trial; a single-centre trial in Haiti. One sub-group post hoc analysis nested in a RCT (SMART trial; a multicentre study in 33 predominantly high income countries) reported reduction of disease progression and serious non-AIDS events when ART was initiated at a CD4 cell count  $< 350$  cells/mm<sup>3</sup> compared with  $< 200$ - $250$  cells/mm<sup>3</sup>.

In the GRADE profile, pooled data from the RCT (816 participants) and the sub-group post hoc analysis (248 participants) provide moderate evidence that starting ART at CD4 levels higher than 200 or 250 cells/mm<sup>3</sup> reduces mortality rates in asymptomatic, ART-naïve, HIV-infected people.

Evidence regarding a reduction in morbidity is less strong as the number of severe adverse events was low.

As the CIPRA HT-001 trial was conducted in a resource-limited setting (RLS), the applicability of these results in determining a change in WHO guidelines is high.

Imprecision (only one RCT), indirectness (post hoc subset analysis) and reporting bias (there may be other trials which did not conduct or publish similar analyses of potential sub-sets within the original trials) are reported in the GRADE profile.

The RCT results are consistent with previous observational cohort studies both from high-income and low-income countries, which showed that early initiation of ART reduces morbidity and mortality. (Sterne 2009; Moh 2007; Badri 2004; Wong 2007). No GRADE tables were produced for these four studies identified in the systematic review as it was felt unlikely that they would increase the overall quality of the evidence.

Considering the uncertain prognostic value of some WHO clinical stage 2 conditions and modelling and observational data suggesting that more than 50% of HIV-infected patients with this clinical stage have a CD4 count of  $< 350$  cells/mm<sup>3</sup>, 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.

#### No uncertainty about the quality of evidence

**Risks/Benefits****Benefits**

- A more permissive CD4 count threshold may provoke a change in treatment seeking behaviour, with a reduction in late presentation and an actual increase in CD4 count at ART initiation.
- Modeling data suggests there is additional transmission benefit (including mother-to-child transmission) from earlier start of ART in populations with high treatment coverage.
- Decreased risk of TB (observational and modeling studies).
- Estimated reduction in mortality of 20% during the 2010-2015 period (if ART coverage is >85%).

**Risks**

- Concerns that starting patients earlier will add burdens to countries and programs by increasing the numbers eligible for ART.
- Risk of inequity in ART access and potential displacement of sicker patients.
- Estimated increased ART cost of 57% 2010-2015 (if ART coverage is >85%).

**Benefits outweigh risks****Values and acceptability****In favour**

- PLHIV highly value earlier initiation of ART.
- Opportunity to reduce the apparent disparity between high- and low-middle income country (LMIC) ART recommendations.
- The recommendations on *when to start* are the same for pregnant women.

**Against**

- Will appear to decrease treatment coverage.
- Potential increased cost needs to be balanced against the high value placed on continued access.
- Potential for more ART related adverse events with earlier start.

**Uncertainty NO****Cost**

- Cost effectiveness of ART is well established.
- Overall costs will increase if initiation of ART is earlier. Long-term incremental benefits seem to justify the cost.

**Uncertainty YES****Feasibility**

- Implementation is dependent on capacity to perform CD4 cell count.
- Need drug combinations which are less toxic if starting patients earlier.
- Feasible with a phased introduction, speed and completeness determined by health system, HIV burden, coverage, capacity & funding.

**Uncertainty YES****Gaps, research needs, comments**

- Currently no commercial point of care CD4 testing available.
- Significant level of uncertainty for cost issues exists and needs further refinement.
- Retention in care/adherence implications of earlier start.
- Impact on health services and health economics.
- WHO will prepare tools to assist countries/programs in the transition to and implementation of the recommendations.
- There are ongoing RCTs evaluating early ART initiation (PROMISE, START, TEMPRANO) some of which will be concluded by 2011/2012.

**Final comment**

In developing these recommendations, the panel placed high value on avoiding death, disease progression including tuberculosis and likely HIV transmission over and above cost and feasibility concerns.