When to start ART in Children and Adolescents

2015 ARV Interim Guidelines

IATT Webinar

October 13, 2015
Background & rationale

• Only 32% of HIV infected children in Sub-Saharan Africa are receiving ART compared to 42% of adults\(^1\).
• Only 50% of HIV exposed infant receive a virological test by their first 2 months of age\(^1\).
• Despite progress in most low- and middle-income countries, many children continue to start cART with severe immunodeficiency\(^2\).
• Overall retention is reported to be poorer prior to ART initiation\(^3\)
• Access to CD4 is limited and reported to be around 50% in several high burden countries\(^4\)
• Limited evidence exists to inform treatment initiation criteria\(^5\)
• Simplification of treatment initiation criteria appears to be critical in enabling paediatric ART scale up\(^4\).

1. UNAIDS 2015 and GARPR 2015
2. Koller et al, JAIDS 2015
4. USAID survey 2015
5. Penazzato, AIDS 2014
## 2013 Recommendations

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>2013 RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 YEAR</td>
<td>Treat ALL&lt;br&gt;Strong recommendation, moderate-quality evidence</td>
</tr>
<tr>
<td>1-5 YEARS</td>
<td>Treat ALL&lt;br&gt;PRIORITY: children &lt; 2 years or WHO stage 3-4 or CD4 count ≤ 750 cells/mm³ or &lt; 25%&lt;br&gt;Conditional recommendation, very-low-quality evidence</td>
</tr>
<tr>
<td>≥5 YEARS</td>
<td>CD4 ≤ 500 cells/mm³&lt;br&gt;Conditional recommendation, very-low-quality evidence&lt;br&gt;CD4 ≤ 350 cells/mm³ as a priority (As in Adults)&lt;br&gt;Strong recommendation, moderate-quality evidence</td>
</tr>
</tbody>
</table>

### CHER trial

- [Graph showing probability of death with different treatment options](#)

### IeDea SA cohort

- [Graph showing follow-up time vs. threshold reached](#)

**Treat ALL less than 5 years to reduce mortality and to remove barriers to ART initiation in children**
Pediatric ART coverage in Rwanda

![Graph showing pediatric ART coverage in Rwanda from 2010 to 2014. The graph indicates a steady increase in the number of children in need of treatment and the percent on treatment. The source is Rwanda TRAC Net System - Spectrum estimates 2014.]

Source: Rwanda TRAC Net System - Spectrum estimates 2014
• ART coverage in children and adolescents below 15 years lags significantly behind

• After 5 years of age the risk of mortality and disease progression is similar to the one estimated for adults, but HIV has been reported as second cause of mortality in adolescents globally

• Increasing evidence that ART impact non-AIDS morbidity such as growth and neurodevelopmental delay.

• Treatment initiation criteria recommended by WHO has been wide adopted in the African region (~70%)

• Limited access to CD4 and poor WHO clinical staging prevent treatment initiation in children and adolescents who are already eligible.

• Some countries (i.e. Uganda, Zambia, Ethiopia, Kenya) are introducing immediate ART for children < 10 or 15 years on programmatic grounds.
Sources of evidence

- Systematic review
- Modelling and Indirect evidence
- Programmatic assessment
Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial

Thanyawee Puthanakit, Yonthanak Saphorn, Jintanat Ananworanich, Pope Kosalaraksa, Rawiwan Hansudewchakul, Ung Vibol, Stephen J Kerr, Suparat Kanjanavanit, Chaiwat Ngampiayskul, Jurai Wongswat, Wicharn Luesomboon, Nicole Ngo-Giang-Huong, Kea Chettra, Theshinee Cheunyam, Tulathip Suwarnlerk, Sasivimol Uboyan, William T Shearer, Robert Paul, Lynne M Mofenson, Lawrence Fox, Matthew G Law, David A Cooper, Praplan Phanuphat, Mean Chhi Vun, Kiat Ruxrunthan, on behalf of the PREDICT Study Group

- No statistically significant difference in critical outcomes
- In PREDICT trial, small but statistically significant differences in terms of changes in weight-for-age and height favouring immediate over deferred treatment
- In PREDICT, a subset of children were assessed for neurodevelopmental outcomes: children in immediate group scored better than deferred
- Greater % ART-related adverse events in immediate versus deferred

QUALITY OF EVIDENCE: LOW
Causal modelling

To use observational data from children aged 5-16 years in the IeDEA-WA, IeDEA-SA and COHERE collaborations to compare

- cumulative mortality and
- growth

- We included ART naive children from 19 cohorts from West and Southern Africa and Europe

- 7,358 children aged 5-10
  (SA: 5753; WA: 1249; Europe: 356)

- 4,553 children aged 10-16
  (SA: 3729; WA: 589; Europe: 235)
Mortality – age 5-10 – present with CD4 $\geq$ 500

Difference ‘immediate ART’ to ‘< 500’:
0.4% (0.02%; 0.6%)
Growth - age 5-10 – present with CD4 ≥ 500

Difference ‘immediate ART’ to ‘< 500’:
0.10 (0.07; 0.12)
Mortality – age 10-16 – present with CD4 $\geq$ 500

Difference ‘immediate ART’ to ‘$< 500$’:
0.1% (-0.6%; 0.9%)
Growth – age 10-16 – present with CD4 $\geq$ 500

**Diagram:**
- Mean HAZ over follow-up time (in months) for different intervention groups:
  - Immediate ART
  - No ART

**Intervention Categories:**
- $<200$
- $<350$
- $<500$
- Immediate ART
- No ART

**Difference ‘immediate ART’ to ‘$<500$’:**
0.05 (-0.002; 0.10)
Conclusions

- Age 5-10: better growth response with earlier treatment initiation, possible mortality benefit for patients presenting with CD4 > 500

- Age 10-16: differences are not so clear, but also smaller sample and wider confidence intervals
Immune Reconstitution

ARROW trial n=1206 (0.4 –17) Initiating ART in children >5 years based on current WHO criteria results in lower CD4 counts in adulthood. HIV-infected children who remain ART-naïve beyond 10 years are unlikely to normalize CD4 count.

Picat, et al PLOS 2013

Figure 3. Predicted long-term CD4 counts in children starting ART at different ages and CD4 levels. (A) CD4 trajectories predicted for children starting ART having reached WHO CD4 count thresholds at age 2 (dashed line), 6 (dotted line), or 10 (dot-dashed line) y. The thin dashed line indicates WHO thresholds for ART initiation, and the thin solid line the trajectory in CD4 count with age expected in a healthy child. (B) Expected CD4 count on immunological maturity (estimated at age 20 y) for different ages and CD4 counts at ART initiation. Values at the ends of the grey contour lines indicate expected adult CD4 count in children starting ART at the ages and CD4 counts given on the horizontal and vertical axes. The black line indicates the current WHO CD4 thresholds for ART initiation. Grey point markers show the age and fitted CD4 count at ART initiation of the 914 children on whom the model is based. They indicate at which ages/CD4 counts the model has substantial evidence, and where it represents an extrapolation from the available data. doi:10.1371/journal.pmed.1001542.g003
Growth delays among HIV infected African children (n=582) enrolled in the Arrow Trial (Szubert, AIDS 2015)
Neurodevelopment

- Early ART initiation of HIV infected children improves mortality and neurodevelopmental (ND) outcomes. (Violari A, NEJM 2008)

- HIV-infected children have worse ND outcomes compared to HIV-uninfected controls. (Ruel TD, CID 2012; Lowick S, Pscy Health Med 2012)

- Difference in ND outcomes among HIV subtypes (A < D) (Boivin et al, JAIDS 2014)

- HIV-positive children, longer duration on ARTs was associated with a reduced risk of impairment in fine motor, receptive language, expressive language and overall global Early Learning Composite score. (Brahmbhatt, JAIDS, 2014)
• Prevent premature death or loss to follow-up
• Enable better immune reconstitution
• Prevent growth delay
• Prevent puberty delay
• Improve neurocognitive outcomes
• Potentially improve school performance
• Avoid future burden to health care system with complications from untreated HIV-related complications

• HIVDR
• Toxicity
• Burden on programmes
Driver of costs is ARVs

**FIGURE 2:** Methods overview: inputs, assumptions and outputs

**TABLE 3:** Average Cost Per Patient Per Year (US$)

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>480.7</td>
<td>496.7</td>
<td>507.3</td>
<td>519.2</td>
<td>590.7</td>
<td>506.7</td>
</tr>
<tr>
<td>10-14</td>
<td>337.3</td>
<td>342.0</td>
<td>345.5</td>
<td>350.0</td>
<td>351.5</td>
<td>345.3</td>
</tr>
<tr>
<td>15-19</td>
<td>236.4</td>
<td>242.9</td>
<td>248.3</td>
<td>261.1</td>
<td>261.9</td>
<td>248.9</td>
</tr>
<tr>
<td>0-14</td>
<td>440.0</td>
<td>448.9</td>
<td>456.0</td>
<td>460.9</td>
<td>464.7</td>
<td>463.9</td>
</tr>
<tr>
<td>0-19</td>
<td>402.9</td>
<td>411.7</td>
<td>415.2</td>
<td>418.6</td>
<td>419.6</td>
<td>413.6</td>
</tr>
</tbody>
</table>

**TABLE 4:** Costs 0-14 (US$ Millions)

<table>
<thead>
<tr>
<th></th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVs</td>
<td>39.3</td>
<td>50.2</td>
<td>50.6</td>
<td>50.6</td>
<td>49.9</td>
<td>240.5</td>
</tr>
<tr>
<td>CTX</td>
<td>1.2</td>
<td>1.5</td>
<td>1.5</td>
<td>1.4</td>
<td>1.4</td>
<td>7.0</td>
</tr>
<tr>
<td>Direct HR</td>
<td>2.4</td>
<td>3.0</td>
<td>2.8</td>
<td>2.8</td>
<td>2.7</td>
<td>13.8</td>
</tr>
<tr>
<td>Lab Commodities</td>
<td>5.9</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.3</td>
<td>35.7</td>
</tr>
<tr>
<td>Total</td>
<td>48.8</td>
<td>62.2</td>
<td>62.6</td>
<td>62.3</td>
<td>61.3</td>
<td>297.0</td>
</tr>
</tbody>
</table>
Community Consultations - Parents and caregivers

• While motivating PLHIV to start treatment may be relatively “easy” to do, staying on and adhering to treatment over the long terms is challenging, particularly for children and adolescent.

• Facilities had insufficient numbers of and trained staff to adequately provide the care and support the treatment needs of their children.

• Services were not perceived as being “child-friendly”; service providers were sometimes unable to deal with side-effects; and they did not understand issues of care-giver consent.

• Psychosocial support for parents and caregivers is required especially to support disclosure to the child.

“I am always crying because I see my child’s health deteriorating” (Parents/Caregivers, Zimbabwe)
Community Consultations
- Adolescents and Young People

• Adolescents and young people voiced being left out of decisions about treatment altogether, often being made without their knowledge of their own status or what the treatment is for.

• This was highlighted as a major barrier for adherence.

“Most of the time I did not take my medication because I had no understanding of what I was drinking.” (Adolescent, Zimbabwe)

• Supportive and sensitive health providers, peer support and sharing experiences especially during transition to adult services is critical for adherence for adolescents.

“Knowing that my peer became a doctor makes me feel that I can also become one.” (Adolescent, Zimbabwe)
Additional unpublished literature
- Adolescent treatment and care

- Y+ global consultation, PATA facility analysis and two multi-country longitudinal qualitative studies (ARROW, BREATHER)

Key themes
- Adherence is an ongoing challenge for adolescents
- Forgetting and being busy are key barriers however many complicated psychosocial issues impact their adherence at different intensities at different times.
- There are limited opportunity for adolescents to discuss their concerns including those beyond ART.
- Poor adherence increases stress: worry, guilt and fear about the impact on their health and also reaction of clinicians.
- Ongoing effective support is critical for adherence – support and environments that provide opportunities for open discussion – through peers and improved attitudes of service providers.
• This intervention is **expected to be feasible** since the number of children and adolescents less than 15 years that are not already eligible based on existing guidance, and current practice is expected to small.

However...

• It will likely put increased demands on supply chain systems and **increased workload** to the human resources.
• **Stock outs** have been observed in several priority countries, including Malawi, Tanzania, Uganda and Zimbabwe.
• Need to strengthen **laboratory monitoring**, particularly virological monitoring given that several children will have initiated ART without baseline CD4 testing and without clinical features of advanced disease.
• Early treatment would mean **more second and third line regimens** being used however options are still limited for children.

The experience of the Ugandan National Programme has highlighted that **despite the efforts made in planning for scale up some key challenges** were encountered. This included ensuring that commodities were available, conducting wide training and ensuring financial support to sustain the effort.
• Expanding ART services will require ensuring retention in care and should be matched with concomitant expansion of interventions to support adherence.
• Ensuring retention in care and adherence to ART, in order to maximize treatment response and minimize HIV drug resistance emergence and transmission.
• Ensuring access to services for adolescent and introducing interventions to support adolescents to remain in care and adhere to ART.
• Determining the baseline CD4 count, as a key monitoring tool to combine with clinical assessment when viral load is not available.
• Careful clinical monitoring remains an essential tool to assess the risk of failure, and lack of laboratory monitoring should therefore never be a barrier to initiating ART.
IN SUMMARY....
Evidence

- **Lack of direct evidence** in support of earlier initiation (particularly for horizontally infected adolescents)\(^1\)

- Indirect evidence suggests **reduction in mortality and improvement in growth** (particularly in children 5-10 years with CD4 >500)\(^2\)

- A growing body of evidence demonstrates the **positive impact of ART** on growth\(^3\), neurodevelopment\(^4\), immunological recovery\(^5\) and in preventing pubertal delays\(^6\)

- Gains appear to be limited for vertically infected **adolescents**\(^2,5\)

---

**References:**

1. Sigfried et al 2014  
2. ieDea network 2015  
3. McGrath et al 2011  
4. Laughton et al 2012  
5. Picat et al 2013  
• **Eliminates the need** for determining CD4 count to initiate ART
• **Avoids delaying** ART in settings without access to CD4 testing.
• **Simplifies** paediatric treatment and facilitate expansion of paediatric ART (task-shifting and decentralization)
• **Improves retention** in care compared to pre-ART

However...need for support to adherence (particularly in adolescents), careful planning, strengthening laboratory services and improvement of procurements and supply of key commodities

Recommendations

- ART should be initiated in all adolescents with HIV regardless of WHO clinical stage and at any CD4 cell count (*conditional recommendation, low-quality evidence*).

- ART should be initiated in all children infected with HIV, regardless of WHO clinical stage or CD4 cell count
  - Infants diagnosed in the first year of life (*strong recommendation, moderate-quality evidence*)
  - Children infected with HIV one year to less than 10 years of age (*conditional recommendation, low-quality evidence*)

<table>
<thead>
<tr>
<th>Age</th>
<th>When you start</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years to less than 19 years</td>
<td>Treat all adolescents individuals with WHO clinical stage 3 or 4 and with CD4 count ≤ 350 cells/mm³ as a priority</td>
</tr>
<tr>
<td>1 year to less than 10 years</td>
<td>Treat all children (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or &lt;25% in younger than 5 years and CD4 count ≤350 cells/mm³ in 5 years and older as a priority)</td>
</tr>
<tr>
<td>Infants (&lt;1 year)</td>
<td>Treat all infants</td>
</tr>
</tbody>
</table>