Managing Children with Advanced HIV disease
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GUIDELINES FOR MANAGING ADVANCED HIV DISEASE AND RAPID INITIATION OF ANTIRETROVIRAL THERAPY
JULY 2017
Introduction

• Why a new guideline in 2017?
• What is ‘advanced disease’ in children?
• How are children with severe disease presenting?
• When to start ART in children?
• What do the new guidelines recommend?
Case

- 12 year old boy
- Generalized lymphadenopathy
- Asymptomatic
- Diagnosed because mom died
- CD4 73, VL – log 5
Figure 1 Proportion of people with advanced HIV disease starting ART by sex and country income group, 2010–2015

The results are based on 951,855 adults from 55 countries after imputation of missing data. The shaded areas represent 95% confidence intervals. Source: IeDEA/COHERE–WHO Collaboration (20)
Background

• 2015 WHO recommends ‘treat all’
• BUT 50% of people still presenting with WHO Stage 3 or 4 of CD4 <200
• High risk of mortality especially if CD4 < 100 at start
• Study in Kenya 191 hospitalized children mortality risk was 61/100 person years with 85% in the first month

1.leDEA and ART Cohort Collaborations ARTC et al. J Acquir Defic Syndr 2014;65:e8-16
EPPICCC
‘European Pregnancy and Paediatric HIV cohort Collaboration’

• ‘Long term trends in mortality and AIDS-defining events after ART start among children and adolescents with perinatal HIV in Europe and Thailand’- Judd et al

• Death: 43/94 deaths (46%) within first 6 months

• First AIDS-defining events in 100/237 (42%) within 6 months after cART initiation
Infants less than 18 months admitted to Tygerberg Children’s Hospital

- Review of PMTCT cascade in hospitalized children
- Median age 5.7 months (3-12.5)
- Admission diagnosis - 55 children: 20 gastroenteritis, 19 pneumonia, 3 SAM, 5 disseminated TB
- 46/55 (83.6%) known exposure prior to pregnancy
- 15/46 (32%) already started ART
- 5/46 (11%) already interrupted ART

With thanks to Elri du Plooy
Masters student
Package of Interventions

Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

What are the issues in children?

- Some data on children older than 5 years from REALITY (only 40 children(2.2%) between 5-12)
- No data in children less than 5 years

1. Can we assume same population: with advanced disease?
2. Are the causes of early morbidity and mortality the same?
3. Are there other differences to consider?
   I. Pill burden
   II. ART Regimen
   III. Programmatic messages
   IV. Children that present after defaulting
Age groups and populations

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these guidelines. Other agencies may use different definitions.

• An adult is a person older than 19 years.
• An adolescent is a person 10–19 years old inclusive.
• A child is a person younger than 10 years old.
• An infant is a child younger than one year of age.
Definitions

- individuals presenting or returning to care with advanced HIV disease (WHO stage 3 or 4 disease and/or CD4 < 200 cells/mm³); such individuals may be ART naive or have interrupted treatment;

- individuals presenting or returning to care when clinically well (absence of WHO clinical stage 3 or 4 disease and/or CD4 cell count ≥200 cells/mm³); such individuals may be ART naive or have interrupted treatment;

- individuals who are clinically stable on ART;¹ and

- individuals receiving an ART regimen that is failing.
Definitions: What is advanced disease in children

**Advanced HIV disease**

- For adults, adolescents, and children ≥ five years, advanced HIV disease is defined as a CD4 cell count <200 cells/mm³ or a WHO clinical stage 3 or 4 event at presentation for care.

- All children with HIV younger than five years old should be considered as having advanced disease at presentation (for rationale, see section 2.2).

- A seriously ill adult or adolescent is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. Other clinical conditions, such as body temperature ≥39°C can also be considered based on local epidemiology and clinical judgement.

- A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as body temperature ≥39°C and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.

- A severely immunosuppressed adult is defined as having a CD4 cell count <50 cells/mm³.

- WHO Clinical Staging is a way to categorize HIV disease severity based on new or recurrent clinical events. There are 4 WHO clinical stages which range from mild symptoms (WHO clinical stage 1) to severe symptoms (WHO clinical stage 4).
### IeDEA Southern Africa Cohort

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Number</th>
<th>WHO Stage at ART Start</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I &amp; 2 (n, %)</td>
</tr>
<tr>
<td>All (0-15 years)</td>
<td>18966</td>
<td></td>
</tr>
<tr>
<td>Severe immunosuppression at ART start</td>
<td>Total number (%)</td>
<td>I &amp; 2 (n, %)</td>
</tr>
<tr>
<td>Yes</td>
<td>4641 (24%)</td>
<td>1816 (39%)</td>
</tr>
<tr>
<td>No</td>
<td>5272 (28%)</td>
<td>2706 (51%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9053 (48%)</td>
<td>3625 (40%)</td>
</tr>
<tr>
<td>&lt; 5 years at presentation</td>
<td>9656</td>
<td></td>
</tr>
<tr>
<td>Severe immunosuppression at ART start</td>
<td>Total number (%)</td>
<td>I &amp; 2 (n, %)</td>
</tr>
<tr>
<td>Yes</td>
<td>2421 (25%)</td>
<td>837 (35%)</td>
</tr>
<tr>
<td>No</td>
<td>2135 (22%)</td>
<td>1518 (48%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5100 (53%)</td>
<td>1942 (38%)</td>
</tr>
<tr>
<td>5-15 years at presentation</td>
<td>9310</td>
<td></td>
</tr>
<tr>
<td>Severe immunosuppression at ART start</td>
<td>Total number (%)</td>
<td>I &amp; 2 (n, %)</td>
</tr>
<tr>
<td>Yes</td>
<td>2220 (24%)</td>
<td>979 (44%)</td>
</tr>
<tr>
<td>No</td>
<td>3137 (34%)</td>
<td>1688 (54%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3953 (42%)</td>
<td>1683 (43%)</td>
</tr>
</tbody>
</table>

### Table 5: CD4 criteria for severe HIV immunodeficiency

<table>
<thead>
<tr>
<th>Immunological marker</th>
<th>Age-specific recommendation to initiate ART $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[A (0)]$^a$</td>
</tr>
<tr>
<td>%CD4</td>
<td>≤11 months</td>
</tr>
<tr>
<td></td>
<td>&lt;25%</td>
</tr>
<tr>
<td>CD4 count</td>
<td>&lt;1500 cells/mm$^3$</td>
</tr>
</tbody>
</table>

$^a$ Strength of recommendation/level of evidence.

$^b$ Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 thresholds are determined by the CD4 reference laboratory performing the test.

$^c$ ART should be initiated by these cut-off levels, regardless of clinical stage, a drop of CD4 below these levels significantly increases the risk of disease progression and mortality.

$^d$ %CD4 is preferred for children aged ≤5 years.
### What causes morbidity/mortality in children on ART?

#### Opportunistic Infections occurring 1 - 90 days after ART start

<table>
<thead>
<tr>
<th>Stage defining disease</th>
<th>All (0-15 years)</th>
<th>Age &lt;5</th>
<th>Age 5-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB (pulmonary and extra-pulmonary)</td>
<td>144</td>
<td>55</td>
<td>89</td>
</tr>
<tr>
<td>Papular pruritic eruptions</td>
<td>98</td>
<td>36</td>
<td>62</td>
</tr>
<tr>
<td>Persistent Generalized Lymphadenopathy</td>
<td>38</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td>Unexplained chronic diarrhoea (&gt;1 month for adults; &gt;14 days for children)</td>
<td>36</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>Unexplained persistent fever (&gt;1 month)</td>
<td>27</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Recurrent oral ulcerations</td>
<td>26</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Unexplained anaemia, and or neutropaenia, and or thrombocytopaenia</td>
<td>23</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Candidiasis (oral) (outside neonatal period)</td>
<td>20</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Bacterial pneumonia, recurrent (&gt;2 episodes within 1 year)</td>
<td>14</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>HIV encephalopathy</td>
<td>9</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Oral hairy leukoplakia</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Kaposi Sarcoma</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Herpes zoster (single dermatome)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoid interstitial pneumonitis</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent or chronic respiratory tract infection</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BCG disease – disseminated</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cryptosporidiosis (duration &gt;1 month)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Herpes simplex virus ulcers (duration &gt;1 month)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Acute necrotising ulcerative stomatitis, gingivitis or periodontitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Gem Patten leDEA

Soutern African International Epidemiologic AIDS
IRIS - P1073

• Prospective observational trial in 202 children less than 72 months of age in Sub-Saharan Africa and India
• Median age was 1.2 (0.5-2.2) years
• 38 (18.8%) had 46 episodes of IRIS
• BCG, TB, dermatological was most common
• Elevated viral load was more important predictor of IRIS than CD4 (LR 10.8 p=0.0001)
• 7 (3.5%) children had complicated IRIS related to TB and cytomegalovirus
• Systemic steroids trended to more IRIS risk (LR 1.72 p=0.19)
Figure 2. Types of IRIS

- BCG
- TB
- Skin
- Candida (oral)
- CMV
- CM

Number of IRIS cases

- Paradoxical
- Unmasking
Supplementary figure 2. Non-IRIS infectious and inflammatory events

Chart Title

Days on ART

Number of events

- Derm
- GE
- Oral Candida
- Other
- Resp
- TB
- UTI

P1073
Cryptococcal Disease

Frequency of CrAg positive samples in patients < 18 years in KwaZulu-Natal 2015 - 2016

821 patients < 18 years (33 positive and 788 negative)

Slide Courtesy of Moherdram Archary
More on cryptococcal meningitis

• Retrospective review of HIV-infected children with cryptococcosis at Tygerberg Hospital from January 2004 through December 2010: 7 children, median age 9.3 years (6.0–13.6) ¹

• A South African laboratory-based survey estimated the incidence of cryptococcosis at 47/100,000 HIV-infected children²

• ARROW³: 7 / 1200 (all > than 7 years)

• P1073: no CM less than 5 years (one case was 5.4 years)

• No cases in children between 5-12 in REALITY at enrolment or during trial

Candida

- REALITY: 1 at enrolment; none during the trial
- P1073: 3 cases of oral candida
- IeDEA: 17 cases in first 3 months
Bacterial infections ? Azithromycin

- Evidence in REALITY trial - no difference in bacterial infections but a decrease in early deaths
- The 1/40 that died in REALITY listed as having died from ‘pneumonia-bacterial’
- In the ARROW trial 9/20 deaths among 0-3 were septicaemia/meningitis
- DDI with lopinavir/ritonavir
- ESBL
### TABLE 1. Incidence Rates* of Death and Bacteremia by cART Exposure Time and TMP-SMX Prophylaxis Regimen

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th></th>
<th></th>
<th>Bacteremias</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person Time (Person Years)</td>
<td>n (per 100 person years)</td>
<td>Incidence Rate Ratio (95% CI)</td>
<td>P†</td>
<td>Incidence Rate (per 100 person years)</td>
<td>Incidence Rate Ratio (95% CI)</td>
<td>P†</td>
</tr>
<tr>
<td>cART exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not on cART</td>
<td>306.3</td>
<td>41</td>
<td>13.4</td>
<td>Ref</td>
<td>26</td>
<td>8.5</td>
<td>Ref</td>
</tr>
<tr>
<td>≤3 mo on cART</td>
<td>43.2</td>
<td>4</td>
<td>9.3</td>
<td>0.69 (0.18–1.90)</td>
<td>0.25</td>
<td>14</td>
<td>32.4</td>
</tr>
<tr>
<td>&gt;3 mo on cART</td>
<td>321.9</td>
<td>8</td>
<td>2.4</td>
<td>0.19 (0.08–0.40)</td>
<td>&lt;0.0001</td>
<td>7</td>
<td>2.2</td>
</tr>
<tr>
<td>TMP-SMX prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>318.31</td>
<td>29</td>
<td>6.80</td>
<td>Ref</td>
<td>13</td>
<td>4.08</td>
<td>Ref</td>
</tr>
<tr>
<td>Thrice weekly</td>
<td>353.02</td>
<td>24</td>
<td>9.11</td>
<td>0.75 (0.41–1.33)</td>
<td>0.15</td>
<td>34</td>
<td>9.63</td>
</tr>
<tr>
<td>Total study</td>
<td>671.33</td>
<td>53</td>
<td>7.89</td>
<td></td>
<td>47</td>
<td>7.00</td>
<td></td>
</tr>
</tbody>
</table>

Values in bold are considered significant (P = 0.05).

* Rates are unadjusted crude rates calculated by dividing number of events by exposure time. Reference categories are “Not on cART” and “Daily prophylaxis.”

† P values refer to the comparison with the reference category.

cART indicates combination anti retroviral therapy; TMP-SMX, trimethoprim-sulphamethoxazole; CI, confidence interval.
Bacterial Infections

- 82 ART naïve children with SAM
- 67% of patients had abnormal white blood cell counts (WBCC) (>12 or <4 \times 10^9/L)
- 70% had elevated CRP
- A pathogen was isolated on the admission blood culture in four patients (6%) and in 27% of urine specimens.
- HAIs were predominately Gram-negative (90%), and 39.5% were extended-spectrum β-lactamase-positive.
- Mortality was not significantly associated with identifying a bacterial pathogen

Other things to consider

- CMV – Ganciclovir
- Viral pneumonia and ventilatory support
- Diarrhoea – Fluid /ORS
- Dermatological conditions
- Growth monitoring and regular follow up
Pill Burden
How it could look?

INH Cotrimoxazole B6

AZT/ABC 3TC Kaletra
When to start ART in children with Severe Acute Malnutrition

- Average age 23.3 months
- Mean time from admission to ART start:
  - Early 5.6 d (SD 4.4)
  - Delayed 23 (SD 5.8)
- No difference in outcomes but earlier improvement in VL, CD4 and growth parameters in delayed arm
- No child died while awaiting ART start
- Recommend: Start ART after two weeks in children with SAM
HIV-infected children 0-12 years were enrolled at 4 hospitals in Nairobi and Kisumu, Kenya, and randomized to receive ART within 48 hours (urgent arm) or 7-14 days (post-stabilization arm)

- 177 randomized
- 57% had weight for age Z-scores of <-2
- CD4 counts were lower in the urgent compared to the post-stabilization arm (12.5% versus 17%, p=0.02)
- Pneumonia, malnutrition and anemia contributed to 61%, 32% and 24% of admission diagnoses, respectively
- Post-randomization, there were 94 severe adverse events including 37 deaths.
- Incidence of mortality was 82.8 per 100 person-years in urgent arm and 60.6 per 100 person-years in post-stabilization arm HR 1.36 95% CI (0.71, 2.60)
- Adjusting for baseline CD4 count, aHR was 1.25 (95% CI 0.65, 2.41).

Njuguna et al CROI 2016
Programmatic Considerations

• Disclosure-time until start
  • Adults/adolescents: median 5 days (IQR 2-8); 558/1765 (31.6%) within two days.
  Children: median 7 days (IQR 4-16); 5/40 (12.5%) within two days. (p=0.002)

• Multiple caregivers

• Importance of ART vs. additional medication

• Pill burden – need FDC but

• Always need single tablet for INH and cotrimoxazole

• More frequent monitoring after starting ART

• Many children will be presenting after defaulting in the future
| Table 1 Components of the package of care for people with advanced HIV disease |
|-------------------------------------------------|----------------|-----------|-----------|-----------|-----------|
| **Intervention**                                 | CD4 cell count | Adults    | Adolescents | Children  |
| Sputum Xpert® MTB/RIF as the first test for TB diagnosis among symptomatic people | Any            | Yes       | Yes        | Yes       |
| LF-LAM for TB diagnosis among people with symptoms and signs of TB | ≤100 cells/mm³  | Yes       | Yes        | Yes       |
| Cryptococcal antigen screening                   | ≤100 cells/mm³ | Yes       | Yes        | No        |
| Co-trimoxazole prophylaxis³                      | <350 cells/mm³ or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections | Yes       | Yes        | Yes*       |
| TB preventive treatment⁴                         | Any            | Yes       | Yes        | Yes*       |
| Fluconazole pre-emptive therapy for cryptococcal antigen-positive people without evidence of meningitis | <100 cells/mm³ | Yes       | Yes        | Not applicable (screening not advised) |
| Rapid ART initiation (as recommended in Chapter 3) | Any            | Yes       | Yes        | Yes       |
| Delay initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3) | Any            | Yes       | Yes        | Yes       |
| Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible | <200 cells/mm³ | Yes       | Yes        | Yes       |

* Limited data available for children. ³ Co-trimoxazole, isoniazid and pyridoxine are available as a fixed-dose combination tablet. ⁴ For children younger than 12 months, only those with a history of TB contact should receive TB preventive treatment if the evaluation shows no TB disease.
Management of advanced HIV disease

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease.

(Strong recommendation, moderate-quality evidence)

Rapid initiation of antiretroviral therapy

Rapid ART initiation\(^a\) should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)

\(^a\)Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start.

(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)
## Recommendations for the package of prophylaxis interventions for people with advanced HIV disease

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Indication to start</th>
<th>Indication to stop</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Co-trimoxazole prophylaxis</td>
<td>Severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or with a CD4 cell count &lt;350 cells/mm³.</td>
<td>Regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage, those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 count ≤350 cells/mm³.</td>
</tr>
<tr>
<td></td>
<td>Same as children</td>
<td>Same as children</td>
</tr>
<tr>
<td>Intervention</td>
<td>Indication to start</td>
<td>Indication to stop</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>TB preventive treatment</td>
<td>Same as adults</td>
<td>After six or at least 36 months according to the recommendation adopted</td>
</tr>
<tr>
<td></td>
<td>Adults, Adolescents, Children</td>
<td>Adults, Adolescents, Children</td>
</tr>
<tr>
<td>Screen with a clinical algorithm; those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered isoniazid preventive therapy. <em>Strong recommendation, moderate-quality evidence</em></td>
<td>Older than 12 months and unlikely to have TB disease on symptom-based screening and no contact with a TB case: six months of isoniazid preventive therapy (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) if they are living in a high TB prevalence setting. <em>Strong recommendation, low-quality evidence</em> Younger than 12 months: only those who have contact with a TB case and TB disease has been ruled out (using investigations) should receive six months of isoniazid preventive therapy. <em>Strong recommendation, low-quality evidence</em></td>
<td>After six months according to the recommendation adopted</td>
</tr>
<tr>
<td>Unknown or positive tuberculin skin test status and unlikely to have active TB: at least six months of isoniazid preventive therapy regardless of the degree of immunosuppression, ART status, prior TB treatment, or pregnancy status. <em>Strong recommendation, high-quality evidence</em></td>
<td>Older than 12 months: those unlikely to have TB disease on symptom-based screening and no contact with a TB case might be offered six months of isoniazid preventive therapy (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) if living in a medium- or low-TB prevalence setting. <em>Conditional recommendation, low-quality evidence</em> All children living with HIV, after successfully completing treatment for TB, should receive isoniazid preventive therapy for an additional 6 months. <em>Conditional recommendation, low-quality evidence</em></td>
<td>After six months according to the recommendation adopted</td>
</tr>
<tr>
<td>In resource-limited settings with high TB incidence and transmission, adults with unknown or positive tuberculin skin test status and in whom active TB has been ruled out: at least 36 months of isoniazid preventive therapy regardless of the degree of immunosuppression, ART status, prior TB treatment, or pregnancy. <em>Strong recommendation, moderate-quality evidence</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Thank you

- Mark Cotton and P1073 team (Stellenbosch, South Africa)
- Marie-Ann Davies, Gem Patten and IeDEA team
- Mo Archary (KZN, South Africa)
- Di Gibb (MRC CTU UK)
- Andy Prendergast (Queen Mary University London)
- George Siberry (PEPFAR)
- Dorothy Mbori-Ngacha (UNICEF)

- Nathan Ford (WHO)
- Helena Rabie (Stellenbosch, South Africa)
Questions

• What are the WHO recommendations for children with advanced disease starting ART?
• Why is fluconazole not part of these recommendations in children less than 5 years?
• What are the main causes of morbidity in children within the first 3 months of starting ART?
• When is the best time to start ART in children less than 5 years?
P1073

• Mark Cotton, Helena Rabie, Elisa Nemes, Hilda Mujuru, Raziya Bobat, Boniface Njau, Avy Violari, Vidya Mave, Charles Mitchell, James Oleske, Bonnie Zimmer, Jennifer L. Ariensen, Elizabeth Smith and Savita Pahwa
Children

The same definition of advanced HIV disease used for adults is applied to children older than five years. Based on data showing that more than 80% of children younger than five years starting ART are WHO clinical stage 3 or 4 and/or have severe immunosuppression, the Guideline Development Group considered all children younger than five years to be eligible for the package for advanced HIV disease (12). The major causes of mortality and morbidity among children with advanced HIV disease remain TB, severe bacterial infections and *Pneumocystis jirovecii* pneumonia but, in contrast with adults, cryptococcal disease is relatively rare. A laboratory-based survey performed in South Africa estimated the incidence of cryptococcal disease to be 47 per 100 000 children living with HIV (34) and within two trial cohorts of children, no cases of cryptococcal disease were reported in children younger than five years (53).
Based on previous recommendations included in the 2016 WHO consolidated ARV guidelines (29), Table 1 outlines the package of screening and prophylaxis interventions for children and adolescents, and Annex 1 provides the detailed recommendations. Increased pill or syrup burden is of particular concern for children, and fixed-dose combinations should be used if possible, including the new fixed-dose combination of co-trimoxazole, isoniazid and pyridoxine. Whether the current package is sufficiently adapted to the specific pathogens causing mortality among children is also of concern, especially to address the high rates of bacteraemia in those younger than three months (54). Further research is needed to determine the components of the package of care for young children and optimal administration and delivery in this age group.

Finally, the routine interventions recommended by WHO for children in general such as deworming, malaria prophylaxis, iron and vitamin A supplementation and growth monitoring should all be provided.