Package Of Care for Children and Adolescents with Advanced HIV Disease: STOP AIDS

Dr. Martina Penazzato
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53% of children living with HIV are receiving treatment compared to 68% of adults

- Only 950,000 children receiving treatment in 2019
- Children living with HIV is declining as children age into adulthood
- Most recent data suggest lower numbers in mid-2020

30% of children and adolescents still present with severe immunosuppression

Source: UNAIDS 2020 Estimates
Tuberculosis, severe bacterial infections remain leading causes of mortality

Ford et al, Lancet HIV 2016
WHO guidelines for Managing Advanced HIV Disease and Rapid Initiation of ART

Advanced HIV disease is defined as CD4 count <200 cells/mm$^3$ or WHO clinical stage 3 or 4 (All children <5 years old considered to have advanced disease)

Evidence that packaged Interventions for advanced disease reduces mortality: REMSTART and REALITY

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)
2017 WHO recommendations for AHD

A package of interventions including:

- screening, treatment and/or prophylaxis for major opportunistic infections,
- rapid ART initiation, and
- intensified adherence support

should be offered to everyone presenting with advanced HIV disease

(strong recommendation, moderate-quality evidence).
2020 AIDS FREE TOOLKIT UPDATES

Supporting countries to advance care for children and adolescent living with HIV
Definition of advanced disease in children: further articulated in 2020 technical brief

**Children > 5 years:**
WHO stage 3 or 4 or a CD4 cell count <200 cells/mm³

**Children < 5 years:**
Considered to have advanced HIV disease

“Although children younger than five years are defined as having advanced disease at presentation, those who have been receiving ART > 1 year and who are clinically stable should not be considered to have advanced disease and should be eligible for multi-month dispensing”
Addressing advanced HIV disease: The difficult part we always forget

Screen
For TB, cryptococcal disease, developmental delay

Treat
For TB, cryptococcal disease, severe pneumonia

Optimize
Early ART initiation within 7 days, optimal regimen (LPV/R or DTG), counselling

Prevent
TB, PJP, cryptococcus, pneumonia and catch-up immunizations

We need to Stop AIDS!

Sources: WHO (2020), Package of CARE for Children and Adolescents with Advanced HIV Disease (AHD): “STOP-AIDS”
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Key components to Screen

Screen

TB
- Screen for TB using a clinical algorithm followed by X-ray when indicated and if available
- Use the following diagnostic tests to confirm TB as applicable:
  - Rapid molecular diagnostic (Xpert® MTB/RIF or Ultra) on (induced) sputum, stool, gastric aspirate or nasopharyngeal aspirate or other extrapulmonary samples if relevant
  - Lateral flow urine lipoarabinomannan (LF-LAM) assay

Cryptococcal infection among adolescents
- Serum or plasma or blood cryptococcal antigen screening followed by lumbar puncture if positive or symptomatic

Malnutrition
- Weight-for-height
- Height-for-age
- Mid-upper arm circumference among children 2–5 years old
Molecular TB testing

Across 140 high-burden developing countries (Cepheid’s HBDC program), over 11,694 devices have been delivered, comprising 52,058 modules.

- Collecting sputum samples can be difficult for children
- Gastric specimens, nasopharyngeal specimens and stool specimens can be considered

<table>
<thead>
<tr>
<th>Max daily throughput (incl. controls)</th>
<th>Abbott m2000sp</th>
<th>Abbott m-PIMA</th>
<th>Cepheid GeneXpert GX-4, 16, 48, 80</th>
<th>Hologic Panther</th>
<th>Roche CAP/CTM 96</th>
<th>Roche 4800/6800/8800</th>
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* Technologies with WHO prequalification listing
* Technologies endorsed by WHO (Global Tuberculosis Program)
* Technologies currently undergoing WHO prequalification review

Information included as of December 20, 2019. Pictures are not to comparable scale.
LF-LAM for screening active TB

Box 2. Recommendations from the LF-LAM guidelines from 2019 (11,12)

For inpatient settings
WHO strongly recommends using LF-LAM to assist in diagnosing active TB among children and adolescents living with HIV
- with signs and symptoms of TB (pulmonary and/or extrapulmonary)
- with advanced HIV disease or who are seriously ill
- regardless of signs and symptoms of TB and with a CD4 count <200 cells/ mm³

For outpatient settings
WHO suggests using LF-LAM to assist in diagnosing active TB among children and adolescents living with HIV
- with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill
- regardless of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm³

WHO recommends against using LF-LAM to assist in diagnosing active TB among children and adolescents
- without assessing TB symptoms
- without TB symptoms and unknown CD4 cell count or without TB symptoms and the CD4 cell count is greater than or equal to 200 cells/mm³
- without TB symptoms and with a CD4 cell count of 100–200 cells/mm³
Screen Key Messages

• Critical and supportive diagnostics exist to support children with advanced HIV disease

• LF-LAM (using urine) is a key diagnostic to identify TB in children

• Molecular TB testing can now use non-sputum specimens for diagnosis

• Rapid and simple cryptococcal antigen testing is now available for diagnosis in adolescents
Addressing advanced HIV disease: The difficult part we always forget

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We need to **Stop AIDS!**

Sources: WHO (2020), Package of CARE for Children and Adolescents with Advanced HIV Disease (AHD): “STOP-AIDS”
Treat: Key messages

- Treatment of TB requires ARVs dose adjustment
- Treatment of severe bacterial infections \((Streptococcus, Staphylococcus, Salmonella)\) and severe pneumonia \((including PCP for infants)\) should follow WHO guidelines
- Malnutrition, main driver of mortality

**Treatment of TB in children living with HIV**

TB Treatment is standard but dose adjustment of ARVs is required
- LPV/r: Super-boosting with additional RTV
- DTG: same dose but twice a day

**Treatment of malnutrition in children living with HIV**

- Should start ART as soon as possible after stabilization of metabolic complications and sepsis
- Should be managed with the same therapeutic feeding approach as HIV negative
- Should receive high dose vitamin A and zinc (included in F-75, F-100 and RUTF)

WHO: Management of severe malnutrition

**Treatment of cryptococcal disease in children:**

- First week:
  - Amphotericin B deoxycolate
  - Fluocytosine
- Second week:
  - Fluconazole
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In a randomized trial from South Africa, young children living with HIV (median age 23 months) with severe acute malnutrition were randomized to receive antiretroviral therapy within 14 days of admission or for antiretroviral therapy to be delayed until nutritional recovery (and after two weeks; median time 23 days) (39). The results suggested that a short delay in antiretroviral therapy initiation during early treatment of acute malnutrition resulted in improved immune recovery, led to more rapid viral suppression and improved anthropometric measures (39). In another randomized trial from Kenya, hospitalized children with HIV (median age 23 months), of which almost half had severe acute malnutrition, were randomized to initiating antiretroviral therapy within 48 hours versus after 7–14 days. The treatment arms did not differ in mortality, and the authors concluded that rapid treatment is safe and that prompt initiation of antiretroviral therapy is essential to reduce the very high mortality observed overall, with 21% of children dying during six months of follow-up (40). Overall, although rapid antiretroviral therapy initiation within seven days of diagnosis is a priority, especially for children older than five years, children who present with severe acute malnutrition or TB or other illnesses that require hospitalization need to be stabilized first. However, initiating antiretroviral therapy is encouraged as part of the child’s hospital admission, since referral after discharge may lead to loss to follow-up and failure to initiate antiretroviral therapy. Similarly, ensuring linkage to the facility where the child will receive ongoing HIV care upon discharge is critical.

Counselling and support

Additional counselling and support are needed with earlier antiretroviral therapy initiation. Counselling tools have been updated to reflect newer optimal regimens and formulations. Adolescents generally face challenges in adhering to medication, and adolescent-friendly services, including enhanced adherence counselling, adolescent peer counsellors and support groups, may be especially valuable.

Useful resources

[Website link for useful resources]

Optimize: Key messages

- Enable rapid ART initiation
- Co-morbidities might require stabilization before ART is started
- ART initiation to happen during admission to reduce LTFU
- Ensure linkage to the facility providing routine care after discharge
- Counselling and support
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Prevent: Key messages

- **Vaccinations**: catch up pneumococcal vaccine but also remember BCG, measles, HPV

- **CTX** for CLHIV remains a core intervention despite scale up of ART

- **6 months INH** remains an effective approach suitable to all children living with HIV, 1HP and 3HP require more data on drug drug interaction with LPVr and DTG to be fully implemented for CLHIV

- **Fluconazole** for adolescents with CrAg positive
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Implementation Considerations (1)

**National**
- As the AHD package is implemented it’s critical to harmonize and align various recommendations adopted by the country
- Registration and procurement of commodities essential step for implementation
- Policies and protocols to enable catch up vaccinations outside of EPI

**Facility**
- Hub-and-spoke model central to current implementation
- Important to enable and support task-shifting for some components of the package
- Ensuring right mix of commodities, screening tools and child-friendly environment at the facility level
- Protocols for referral

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**National level**
- The recommendations in the 2017 guidelines on advanced HIV disease (AHD) (and other related updated WHO guidelines) need to be adopted in national policy and guidelines.
- It is important to try to align recommendations across multiple guidelines relating not only to HIV (for example, TB and HIV guidelines relating to TB preventive treatment) but also to routine child health and development interventions (vitamin A, deworming and Expanded Programme on Immunization).
- Registration and procurement of the required commodities and medication (especially formulations for children) are vital to implementing services for advanced HIV disease for children and adolescents (see table 4 for pricing for some key AHD commodities).
- Policies and/or standard operating procedures to enable catch-up vaccination outside the Expanded Programme on Immunization schedule for children living with HIV need to be available.

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**Facility level**
- Currently, the advanced HIV disease package is being implemented as a hub-and-spoke model. Further guidance on this is available in the global advanced HIV disease toolkit (http://www.differentiatedcare.org/Resources/Resource-Library/Global-Advanced-HIV-Disease-toolkit).
- In the context of ongoing and enhanced efforts to ensure task shifting for services for children, all cadres of health-care workers need training for certain components of the package such as screening and enhanced antiretroviral therapy counselling.
- Centres introducing the advanced HIV disease package for children should provide a child-friendly environment.
- Child-specific resources such as a mid-upper arm circumference tape, stadiometer, appropriate scales and expertise in pediatric phlebotomy should be available.
- A specific child-friendly space could be used as an opportunity to educate on early childhood development and sensitization to components of the advanced HIV disease package (https://www.who.int/maternal-child_adolescent/child/multiplying-care-framework/en/).
- Ensure an appropriate mix of TB preventive treatment regimens based on the age distribution of children and adolescents. Consider how many children are receiving a regimen based on protease inhibitor or integrase inhibitors, since they will need six months of isoniazid rather than a regimen based on RH, 3HP or 1HP. Anticipate the correct mix of commodities based on age and regimens.
- Protocols for referral up, down and across should be in place: for example, safe administration of amphotericin B may require referral to a centre with a minimum package of preventing, monitoring and managing toxicity.
Implementation Considerations (2)

**Health care providers**
- Training, capacity building and supported supervision (inclusion of AHD package in training curriculum)
- Limited access to specific diagnostic tools should not prevent clinical diagnosis and treatment

**Laboratory**
- Ensuring SOPs are in place as well as training, capacity building activities (i.e. sample collection for TB screening)
- Explore capacity for AMR surveillance

**Monitoring**
- Drug toxicity
- Ensuring development of tools to tackle implementation of the package
Research gaps

Clinical research

Diagnostics
- Research gaps related to diagnostics in children include the need to develop simplified point-of-care diagnostics for pneumonia, specifically Pneumocystis pneumonia and cytomegalovirus disease.
- In addition, the use of rapid molecular tests in stools and other urine LAM assays needs to be further evaluated in children.

Prophylaxis
- Whether there is an optimal package of prophylactic interventions for children living with HIV younger than five years has yet to be determined. This may focus on bacterial infections and specifically on the benefit of azithromycin.
- TB preventive treatment using 3HP and 1HP is currently being studied among younger children. It is especially important to ensure the safe use of rifamycin-containing TB preventive treatment in conjunction with DTG (https://clinicaltrials.gov/ct2/show/NCT03730181 https://www.imaactnetwork.org/studies/IMAACT2024.asp).
- Research gaps related to prophylaxis include the evaluation of TB preventive treatment among children living with HIV younger than one year.

Treatment
- There is an urgent need to confirm that double-dose DTG will enable therapeutic levels and is safe in children who weigh <25 kg and are co-treated with rifampicin.
- Research gaps related to treatment include the treatment of pneumonia and whether empirical treatment of TB and/or cytomegalovirus should be initiated among children living with HIV who present with severe pneumonia. In addition, the most appropriate timing to initiate antiretroviral therapy during nutritional rehabilitation is also being studied in the EMPIRICAL trial (EMPIRICAL: https://penta-id.org/hiv/empirical).
- Single-dose liposomal amphotericin B (in addition to flucytosine and fluconazole) is being studied in adults and may have implications for adolescents and older children with cryptococcal meningitis (AMBITION: https://doi.org/10.1186/s13001-024-0064).

Operational research
The AIDS Free Working Group is pleased to announce the launch of an updated version of the AIDS Free toolkit for the acceleration of testing and treatment scale-up in children and adolescents living with HIV.

Available at:
http://www.who.int/hiv/pub/paediatric/aids-free-toolkit/en/
http://www.who.int/hiv/pub/paediatric/aids-free-toolkit/fr/

New elements include:

- Policy Brief: Considerations for introducing new antiretroviral drug formulations for children (July 2020)
- Policy Brief: Improving strategic information to strengthen programmes and accelerate progress toward paediatric and adolescents’ global targets and impact goals
- Package of care for children and adolescents with advanced HIV disease (AHD): “STOP-AIDS”
- Nurturing care for children affected by HIV

AIDS Free

1. Advocacy
2. Diagnosis
3. Drug Optimization
4. Service Delivery
5. Community Engagement
6. Monitoring and Evaluation
Useful resources (1)


Useful resources (2)


Thank you

WHO
20, Avenue Appia
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Switzerland

www.who.int
www.gap-f.org/
www.who.int/hiv/pub/paediatric/aids-free-toolkit/en/