

Overview of the WHO guidelines on Advanced HIV disease in children

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What is advanced HIV disease?

For adults, adolescents, and children \geq five years old, 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

- “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”

Key global statistics for Advanced HIV disease and opportunistic infections

630,000

AIDS-RELATED DEATHS IN
2022

>20-30%

AHD AT BASELINE,
SOMETIMES HIGHER
(UPTO 50%)

187,000

DEATHS FROM TB AMONG
PLHIV IN 2021

112,000

DEATHS FROM
CRYPTOCOCCAL INFECTION
IN 2021

380,000

AIDS-RELATED DEATHS IN
THE WHO AFRICAN
REGION

1.5M

CHILDREN LIVING WITH
HIV

84,000

AIDS-RELATED DEATHS IN
CHILDREN WITH HIV

4.3M

ADULTS LIVING WITH AHD

Key challenges with pediatric advanced HIV disease



Lack of timely identification

limited or no routine surveillance

Poor linkage to care

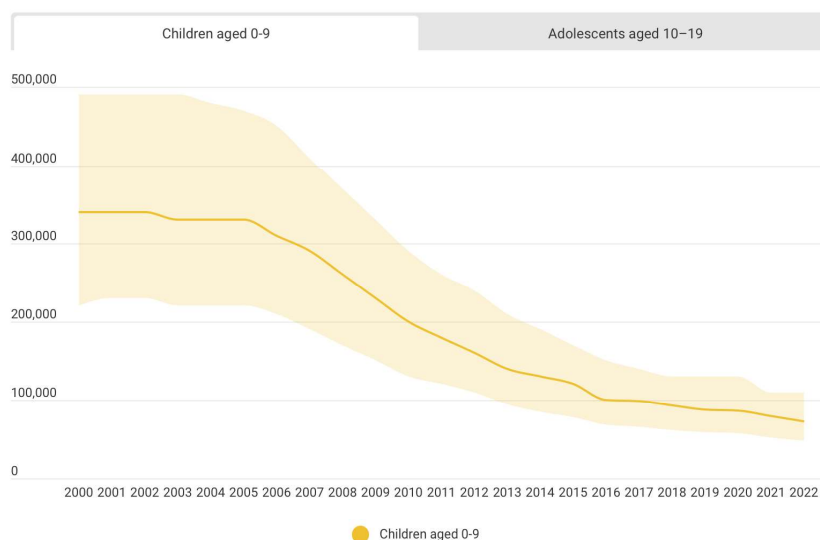
Limited access to appropriate formulation

Lagging behind adults in the "Treat All era"

Malnutrition key driver of mortality

While tremendous strides have been made in early childhood survival for children living with HIV, adolescents are being left behind

Number of AIDS-related deaths among children aged 0–9 years and adolescents aged 10–19 years, 2000–2022

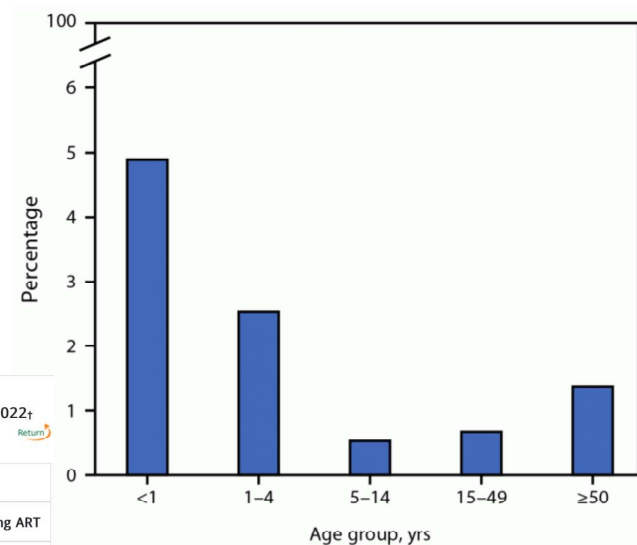


What do we know about pediatric AIDS-related mortality?

- Data from 28 countries showed the highest mortality rates, despite receiving ART – i.e., Under-5s showed a significantly greater rate of mortality or treatment interruptions in 2021-2022.
- 50% of children are estimated to die by the age of two years without ART

TABLE 1. Annual proportion of reported deaths and crude mortality ratios among persons living with HIV and receiving antiretroviral treatment — U.S. President's Emergency Plan for AIDS Relief, 28 supported countries and regions,* 2021–2022†

Characteristic	2021			2022			2021 and 2022 (annual mean) [§]		
	% Died	No. died	No. receiving ART	% Died	No. died	No. receiving ART	% Died	No. died	No. receiving ART
Age group, yrs									
<1	4.4	585	13,223	5.5	587	10,737	4.9	586	11,980
1–4	2.6	2,786	108,325	2.5	2,581	102,695	2.5	2,684	105,510
5–14	0.5	2,943	537,867	0.5	2,772	534,105	0.5	2,858	535,986
15–49	0.7	94,539	13,089,351	0.6	90,672	13,984,027	0.7	92,606	13,536,689
≥50	1.4	50,001	3,488,945	1.3	51,913	3,936,499	1.4	50,957	3,712,722
Total	0.9	150,854	17,237,711	0.8	148,525	18,568,063	0.8	149,691	17,902,887



- A study from Ethiopia found a significant association with malnutrition at baseline, stage ⅓ illness at presentation, poor ART adherence, no prior isoniazid prophylaxis with increased mortality.

Mekonnen GB, Birhane BM, Engdaw MT, Kindie W, Ayele AD, Wondim A. Predictors of a high incidence of opportunistic infections among HIV-infected children receiving antiretroviral therapy at Amhara regional state comprehensive specialized hospitals, Ethiopia: A multicenter institution-based retrospective follow-up study. *Frontiers in Pediatrics*. 2023 May 2;11:1107321.

Agathis NT. Mortality Among Children Aged 5 Years Living with HIV Who Are Receiving Antiretroviral Treatment—US President's Emergency Plan for AIDS Relief, 28 Supported Countries and Regions, October 2020–September 2022. *MMWR. Morbidity and Mortality Weekly Report*. 2023;72.

Common causes of hospitalization

- Bacterial infections, AIDS-related illness, hematological and malnutrition were among leading causes of admission in children with HIV

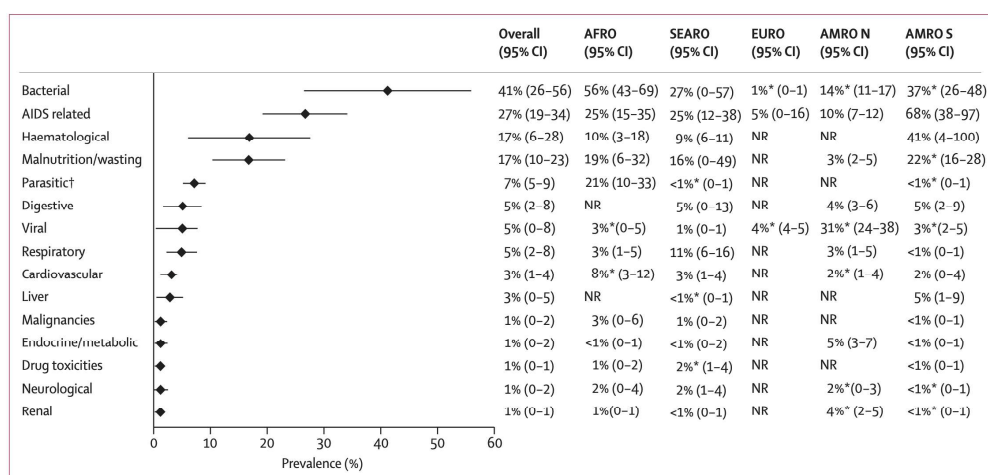


Figure 3: Causes of hospital admission in children

AFRO=African region. AMRO N=region of the Americas (North). AMRO S=region of the Americas (South and Central). EURO=European region. EMRO=eastern Mediterranean region. NR=not reported. SEARO=southeast Asia region. WPRO=western Pacific region. *Only one study contributed to the estimate. †Mainly malaria.

Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ, Davies MA, Vitoria M, Penazzato M, Nsanzimana S, Frigati L. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. The lancet HIV. 2015 Oct 1;2(10):e438-44.

What are the most common causes of death?

- Minimally invasive tissue sampling was performed in 176 decedents in western Kenya at a surveillance site.
- 14% (n = 25) were HIV-positive, median viral load was 112 205 copies/ml [interquartile range (IQR) = 9349–2 670 143].
- HIV-disease (96%; n = 24) and malnutrition (23%; n = 34) were the leading underlying causes of death in HIV-infected and HIV-uninfected decedents, respectively.
- Malnutrition was more frequent in HIV-positive (56%; n = 14) than HIV-negative decedents (31%; n = 49) (P value = 0.03).
- Viral pneumonia was twice as common in HIV-infected (50%; n = 9) than HIV-uninfected decedents (22%; n = 7) (P value = 0.04).

Viral load suppression

Children lag behind adults in terms of viral load suppression

This greatly increases the risk of failing on treatment, as well as the development of opportunistic infections – pneumonia, bacterial infections, diarrhoeal illness, tuberculosis and also bloodstream infections.

Viral load suppression ^{ss}			
Age group, yrs		num	denom
<1	78.4	2,687	3,427
1–4	73.2	48,106	65,742
5–14	85.0	367,312	431,988
15–49	94.3	9,279,763	9,836,384
≥50	96.3	2,830,747	2,940,808

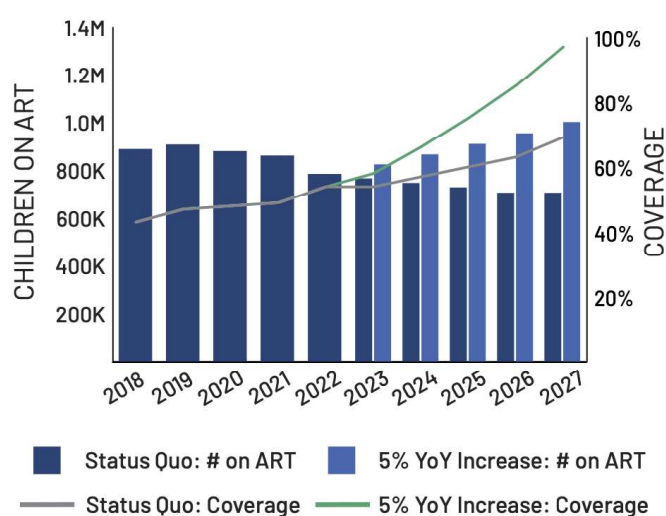
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Access to DTG continues to be a challenge - but is a solvable problem

DTG based formulation have been gradually scaled out over the past 2 years

It is approximated that around 62% of ART provided to children with HIV is DTG-based, based on data from 17 countries

pDTG is a favorable formulation – contributing to improved adherence, as well as viral suppression



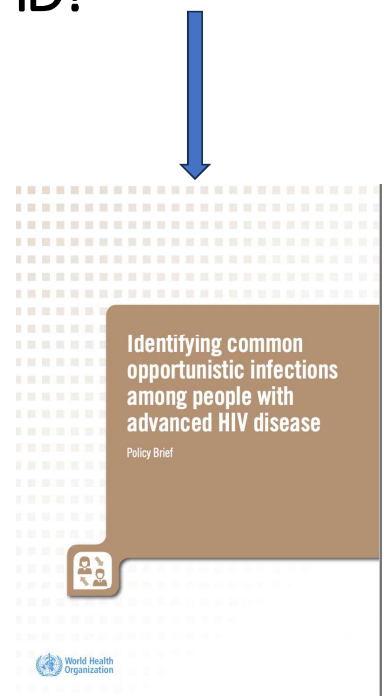
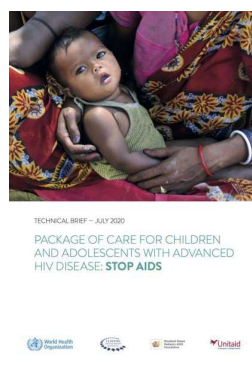
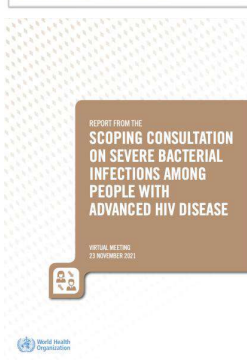
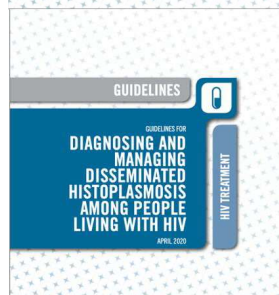
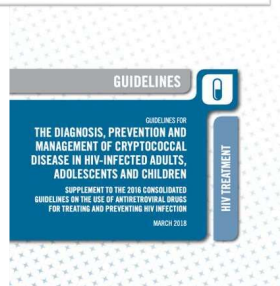
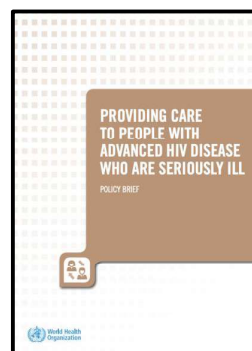
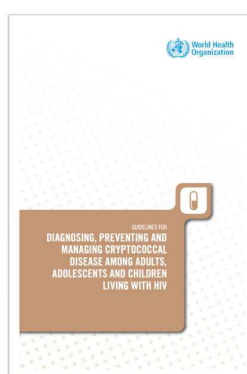
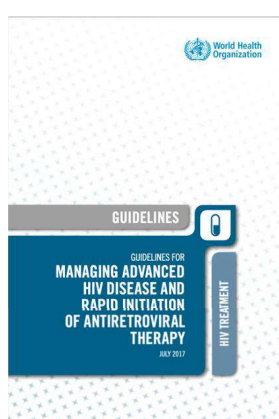
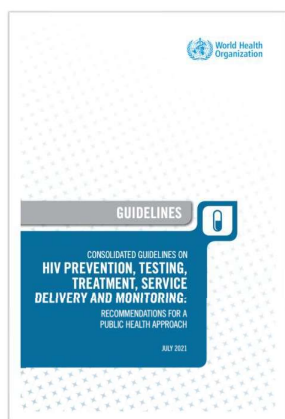
percent.^{i,iii} If the current stagnant and downward trends in both case-finding and retention continue, CHAI estimates that pediatric ART coverage in GA LMICs will only reach 69 percent in 2027. However, achieving a five percent year-over-year (YoY) increase in the number of CLHIV on ART could drastically increase pediatric coverage to close to 100 percent by 2027 [Figure 31].

WHO-Recommendation for advanced HIV disease

Recommendation (2017)

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-certainty evidence*).

What guidelines/policies does WHO have on AHD?



Addressing advanced HIV disease in children: “It’s not just about ART”



30% of children and adolescents still present with severe immunosuppression

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

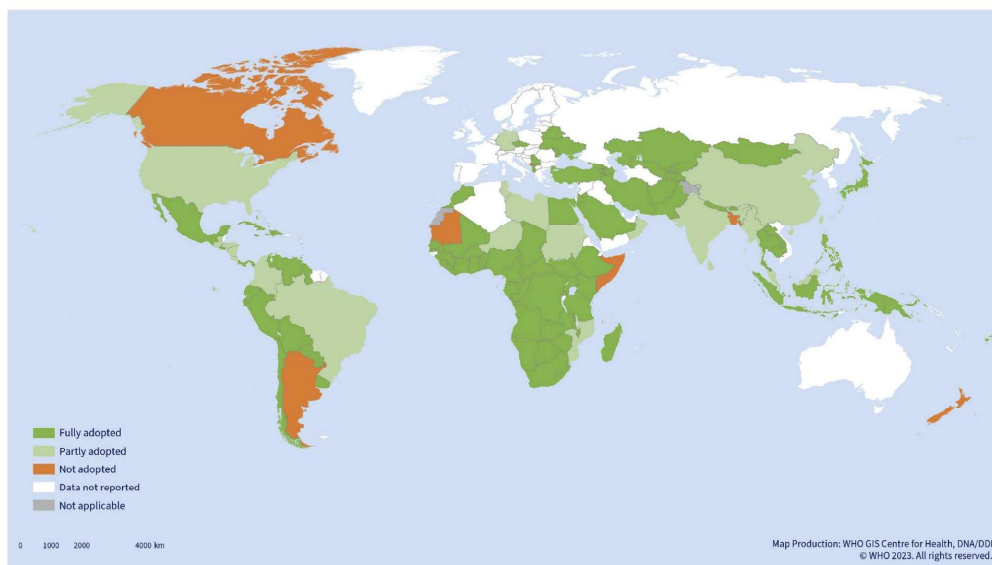
Prevent

TB, PJP, cryptococcal meningitis, pneumonia and catch-up immunizations

We need to Stop AIDS!

Global uptake of the AHD package of care

Adoption of the 2021 WHO recommendation to offer a package of interventions to everyone presenting with advanced HIV disease, as of July 2023



Sources: Global AIDS Monitoring (UNAIDS/WHO/UNICEF) and WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, 2023.

Implementing the STOP-AIDS package

Intervention	Component	<5 years	5–9 years	10–19 years
Screening and diagnosis	Screen for TB using clinical algorithm followed by X-ray when indicated and if available Xpert® MTR/RIF or Xpert® Ultra assay as the first test (Induced or expectorated) sputum, gastric aspirate, stool or nasopharyngeal aspirate or other extrapulmonary specimens (induced or expectorated)	Yes	Yes	Yes
	LF-LAM assay ^a	Yes	Yes	Yes
	Cryptococcal antigen screening (Specimen: Serum, plasma, or whole blood) If blood cryptococcal antigen positive or symptomatic, lumbar puncture	No	No	Yes
Prevention, prophylaxis and pre-emptive treatment	Pneumococcal conjugate vaccine (catch-up)	Yes	No	No
	Co-trimoxazole ^b	Yes	Yes	Yes
	TB preventive treatment	Yes	Yes	Yes
	Fluconazole pre-emptive therapy for cryptococcal antigen-positive without evidence of meningitis ^c	Not applicable	Not applicable	Yes

^a See Box 2 (11,12).

^b See text for when to discontinue.

^c Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen-positive adolescents to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating antiretroviral therapy for adolescents living with HIV who have a CD4 cell count <100 cells/mm³ (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of <200 cells/mm³ (conditional recommendation; moderate certainty evidence). When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adolescents living with HIV who have a CD4 cell count <100 cells/mm³ (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of <200 cells/mm³ (conditional recommendation; moderate certainty evidence). Screening and primary prophylaxis are not recommended for children younger than 10 years, given the low incidence of cryptococcal meningitis in this age group (13).

Box 1. Screen, Treat, Optimize and Prevent AIDS

Screen^a

TB

- Screen for TB using a clinical algorithm^b followed by X-ray when indicated and if available
- Use the following diagnostic tests to confirm TB as applicable:^c
 - Rapid molecular diagnostic (Xpert® MTR/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^d

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

Treat

TB, severe pneumonia, severe bacterial infections, cryptococcal meningitis and severe acute malnutrition according to WHO guidelines

Optimize

Rapid antiretroviral therapy start – within seven days with optimal regimens^e
Antiretroviral therapy counselling

Prevent

Bacterial infections and *Pneumocystis pneumonia*
Co-trimoxazole prophylaxis

TB

- TB preventive treatment

Cryptococcal meningitis among adolescents

- Fluconazole pre-emptive therapy

Vaccinations

- Pneumococcal vaccine
- Human papillomavirus
- Measles
- BCG



^a Screening refers to screening and diagnostics throughout this publication.

^b See Fig. 3 in Guidance for national tuberculosis programmes on the management of tuberculosis in children (9).

^c A negative test result does not exclude TB in children living with HIV in whom there is a strong clinical suspicion of TB.

^d See Table 2 and the text for recommendations.

^e Unless TB or cryptococcal disease is diagnosed (10).

Conclusion

- All the necessary guidance, tools, and interventions are already available
- Implementing these in high burden settings is a priority
- Understanding the specific challenges that CHIV face is critical
- Rapid identification and linkage to ART is critical
- Screening and management of OIs is critical

Thank you