Managing Children with Advanced HIV disease

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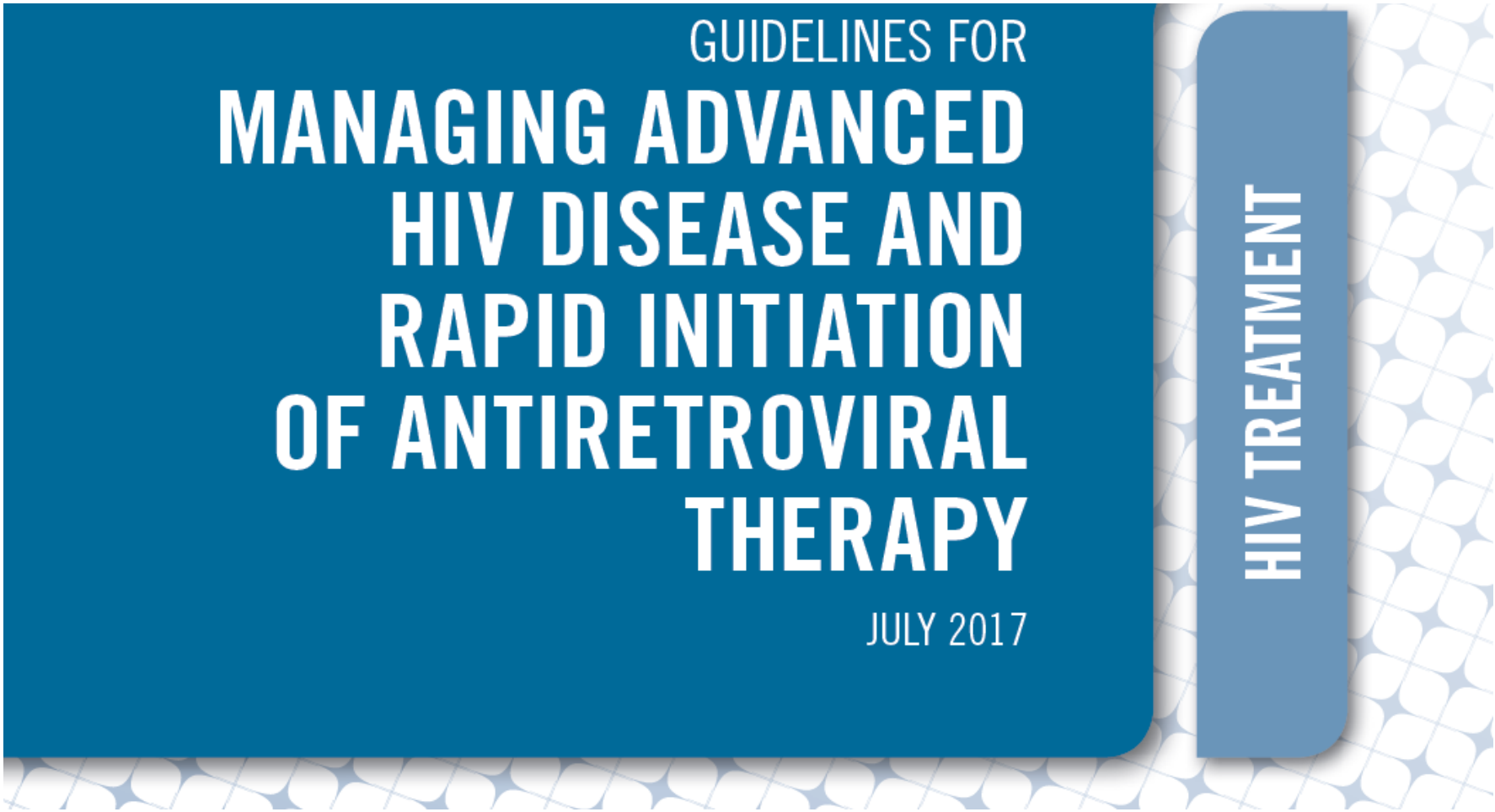
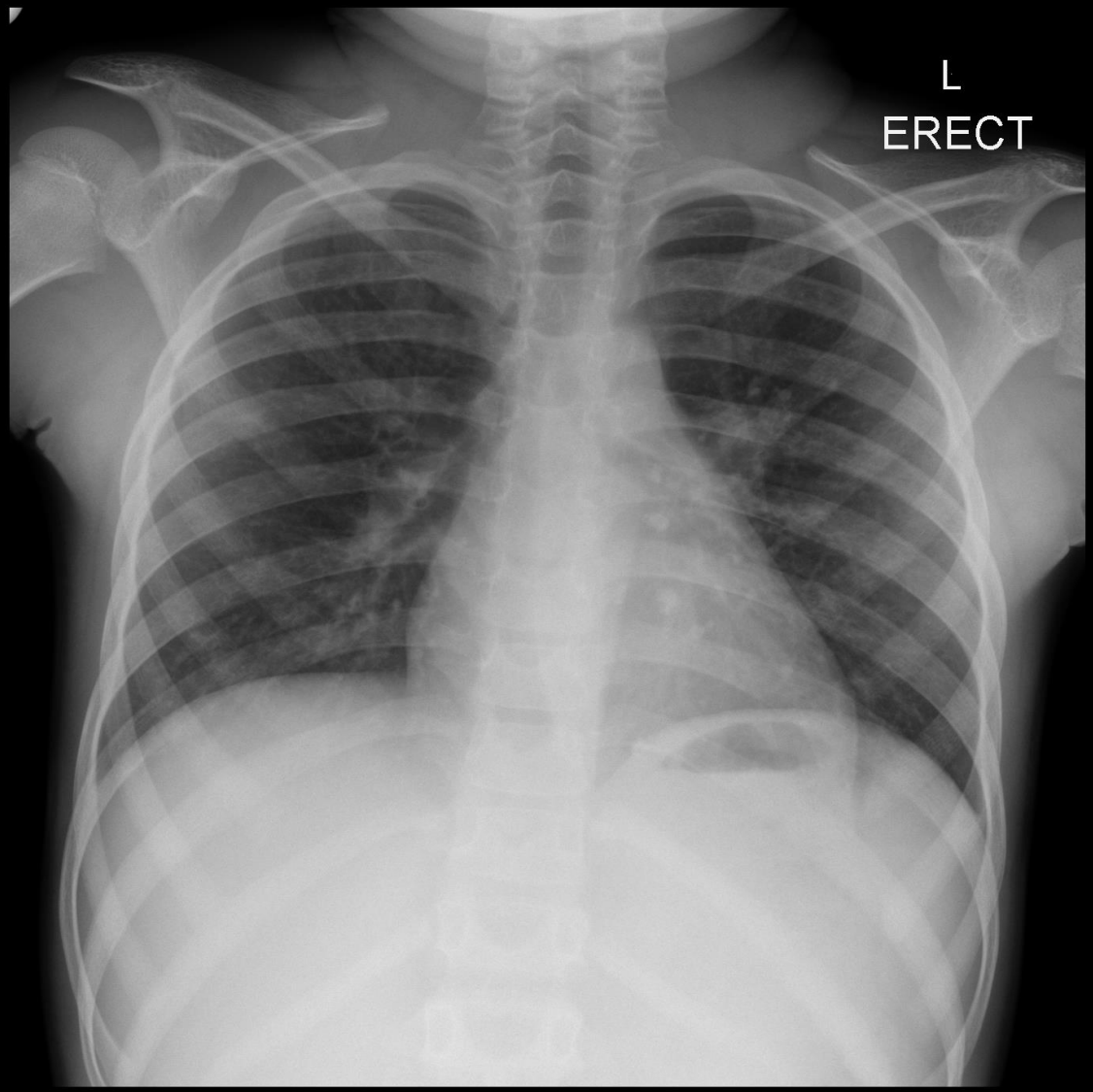


Introduction

- 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 lynphadenopathy
- Asymptomatic
- Diagnosed because mom died
- CD4 73, VL – log 5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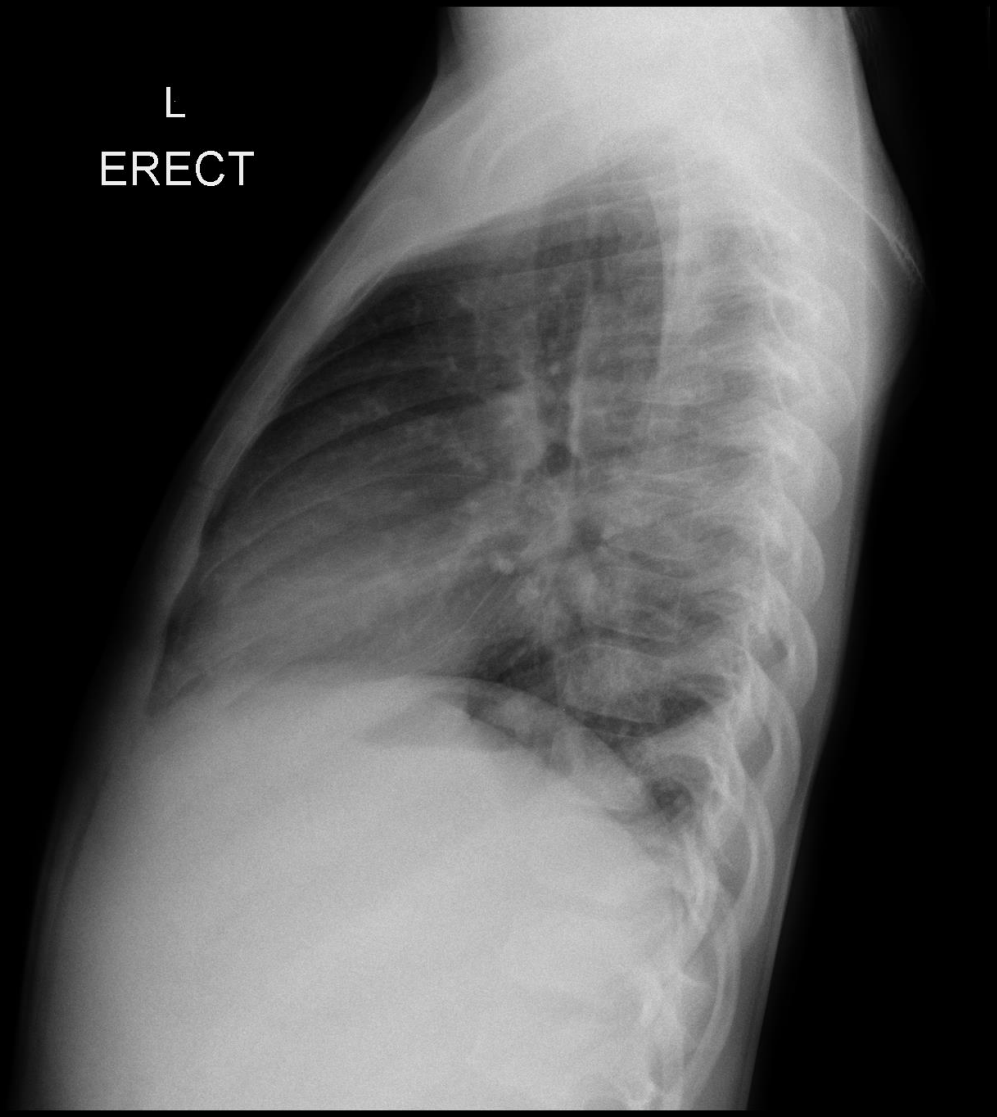
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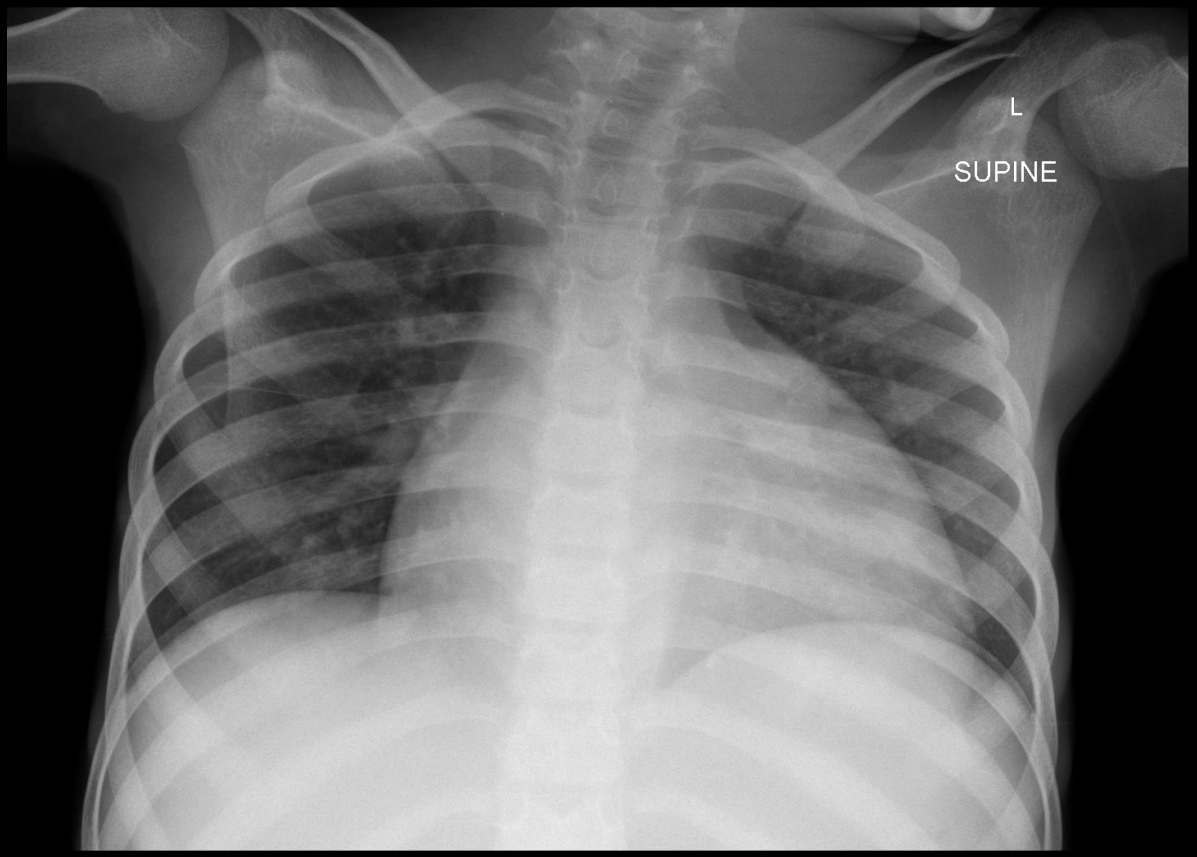
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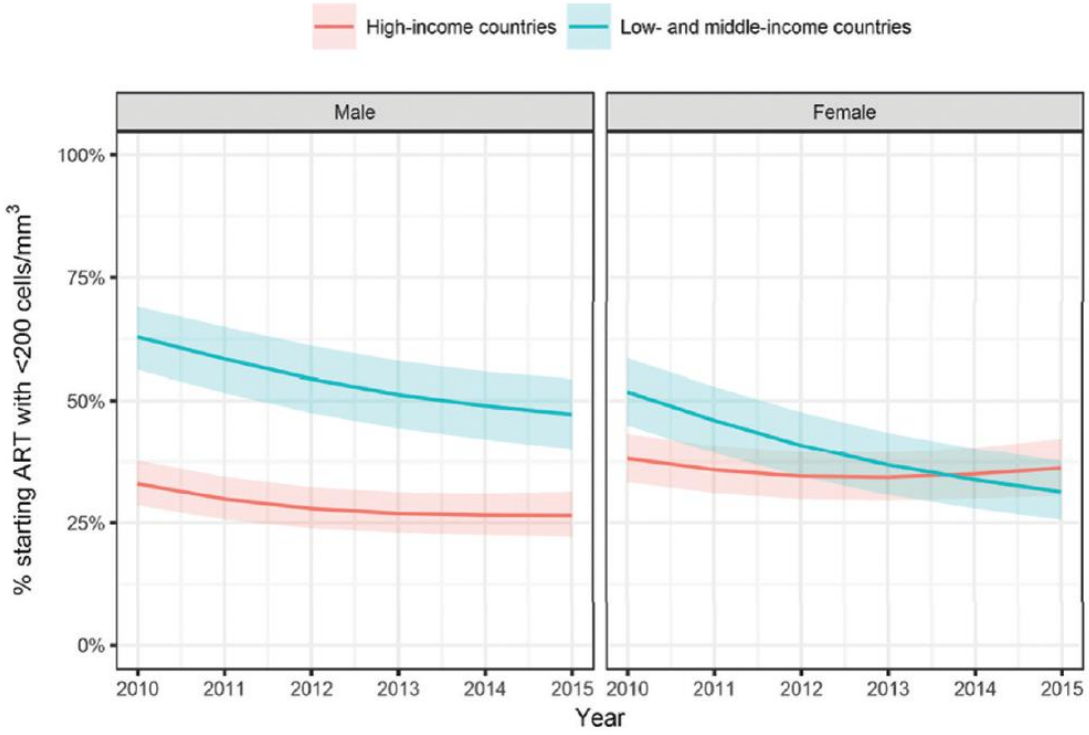
SUPINE

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 CD 4 <200 [1]
- High risk of mortality especially if CD4 < 100 at start [2]
- 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
2.Walker AS et al. Clin Infect Dis 2012 55:1707-18

EPPICC

'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

Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial

*Sayoki Mfinanga, Duncan Chanda, Sokoine L Kivuya, Lorna Guinness, Christian Bottomley, Victoria Simms, Carol Chijoka, Ayubu Masasi, Godfather Kimaro, Bernard Ngowi, Amos Kahwa, Peter Mwaba, Thomas S Harrison, Saidi Egwaga, Shabbar Jaffar, on behalf of the REMSTART trial team**

ORIGINAL ARTICLE

Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa

J. Hakim, V. Musiime, A.J. Szubert, J. Mallewa, A. Siika, C. Agutu, S. Walker, S.L. Pett, M. Bwakura-Dangarembizi, A. Lugemwa, S. Kaunda, M. Karoney, G. Musoro, S. Kabahenda, K. Nathoo, K. Maitland, A. Griffiths, M.J. Thomason, C. Kityo, P. Mugyenyi, A.J. Prendergast, A.S. Walker, and D.M. Gibb, for the REALITY Trial Team*

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

Definitions

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/mm^3); 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/mm^3); 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

All (0-15 years)	18966		**WHO Stage at ART start**		
Severe immunosuppression at ART start	Total number (%)		I & 2 (n, %)	3 & 4 (n, %)	Unknown (n, %)
Yes	4641	24%	1816 (39%)	1920 (41%)	905 (20%)
No	5272	28%	2706 (51%)	1515 (29%)	1051 (20%)
Unknown	9053	48%	3625 (40%)	3195 (35%)	2233 (25%)
< 5 years at presentation	9656		**WHO Stage at ART start**		
Severe immunosuppression at ART start	Total number (%)		I & 2 (n, %)	3 & 4 (n, %)	Unknown (n, %)
Yes	2421	25%	837 (35%)	1075 (44%)	509 (21%)
No	2135	22%	1018 (48%)	644 (30%)	473 (22%)
Unknown	5100	53%	1942 (38%)	1886 (37%)	1272 (25%)
5-15 years at presentation	9310		**WHO Stage at ART start**		
Severe immunosuppression at ART start	Total number (%)		I & 2 (n, %)	3 & 4 (n, %)	Unknown (n, %)
Yes	2220	24%	979 (44%)	845 (38%)	396 (18%)
No	3137	34%	1688 (54%)	871 (28%)	578 (18%)
Unknown	3953	42%	1683 (43%)	1309 (33%)	961 (24%)

Table 5. CD4 criteria for severe HIV immunodeficiency

Immunological marker[a]	Age-specific recommendation to initiate ART[b] [A (I)]*			
	≤11 months	12 months to 35 months	36 months to 59 months	≥5 years
%CD4+[c]	<25%	<20%	<15%	<15%
CD4 count[c]	<1500 cells/mm³	<750 cells/mm³	<350 cells/mm³	<200 cells/mm³

* Strength of recommendation/level of evidence.
a Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilization of acute presenting conditions.
b 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.
c %CD4+ is preferred for children aged <5 years.

IeDEA Southern Africa
International epidemiologic Databases to Evaluate AIDS

What causes morbidity/mortality in children on ART?

Opportunistic Infections occurring 1 - 90 days after ART start	Number of occurrences between 1 and 90 days after ART start		
Stage defining disease	**All (0-15 years)**	**Age <5**	**Age 5-15**
TB (pulmonary and extra-pulmonary)	144	55	89
Papular pruritic eruptions	98	36	62
Persistent Generalized Lymphadenopathy	38	15	23
Unexplained chronic diarrhoea (> 1month for adults; >14 days for children)	36	17	19
Unexplained persistent fever (> 1 month)	27	12	15
Recurrent oral ulcerations	26	10	16
Unexplained anaemia, and or neutropaenia , and or thrombocytopaenia	23	8	15
Candidiasis (oral) (outside neonatal period)	20	17	3
Bacterial pneumonia, recurrent (>2 episodes within 1 year)	14	9	5
HIV encephalopathy	9	8	1
Oral hairy leukoplakia	6	4	2
Kaposi Sarcoma	3	0	3
Herpes zoster (single dermatome)	2	0	2
Lymphoid interstitial pneumonitis	2	1	1
Recurrent or chronic respiratory tract infection	2	1	1
BCG disease – disseminated	1	1	0
Cryptosporidiosis (duration > 1 month)	1	0	1
Herpes simplex virus ulcers (duration > 1 month)	1	0	1
Acute necrotising ulcerative stomatitis, gingivitis or periodontitis	1	0	1
Seborrheic dermatitis	1	1	0

IeDEA Southern Africa
International epidemiologic Databases to Evaluate AIDS

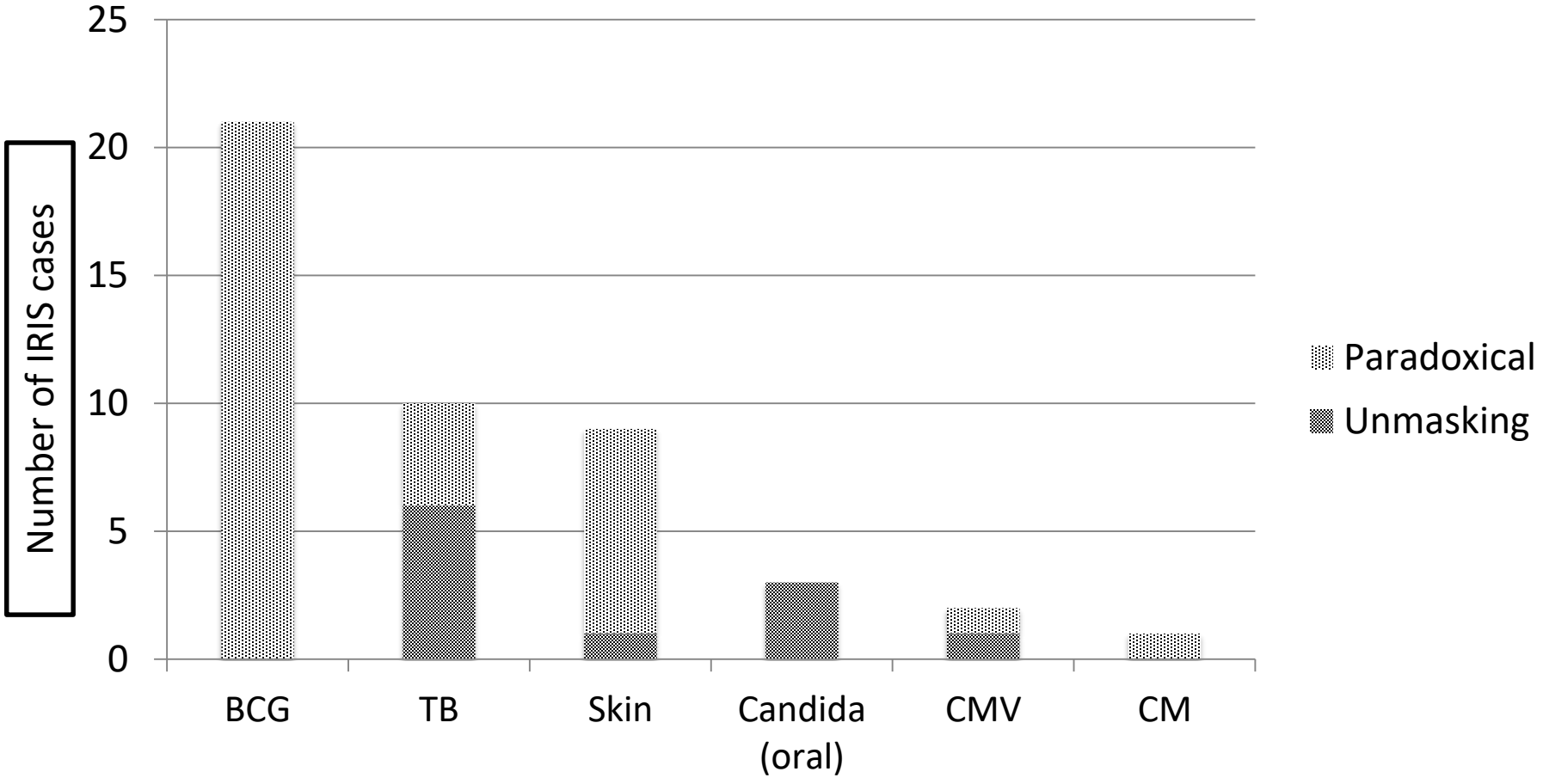
Gem Patten IeDEA

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)

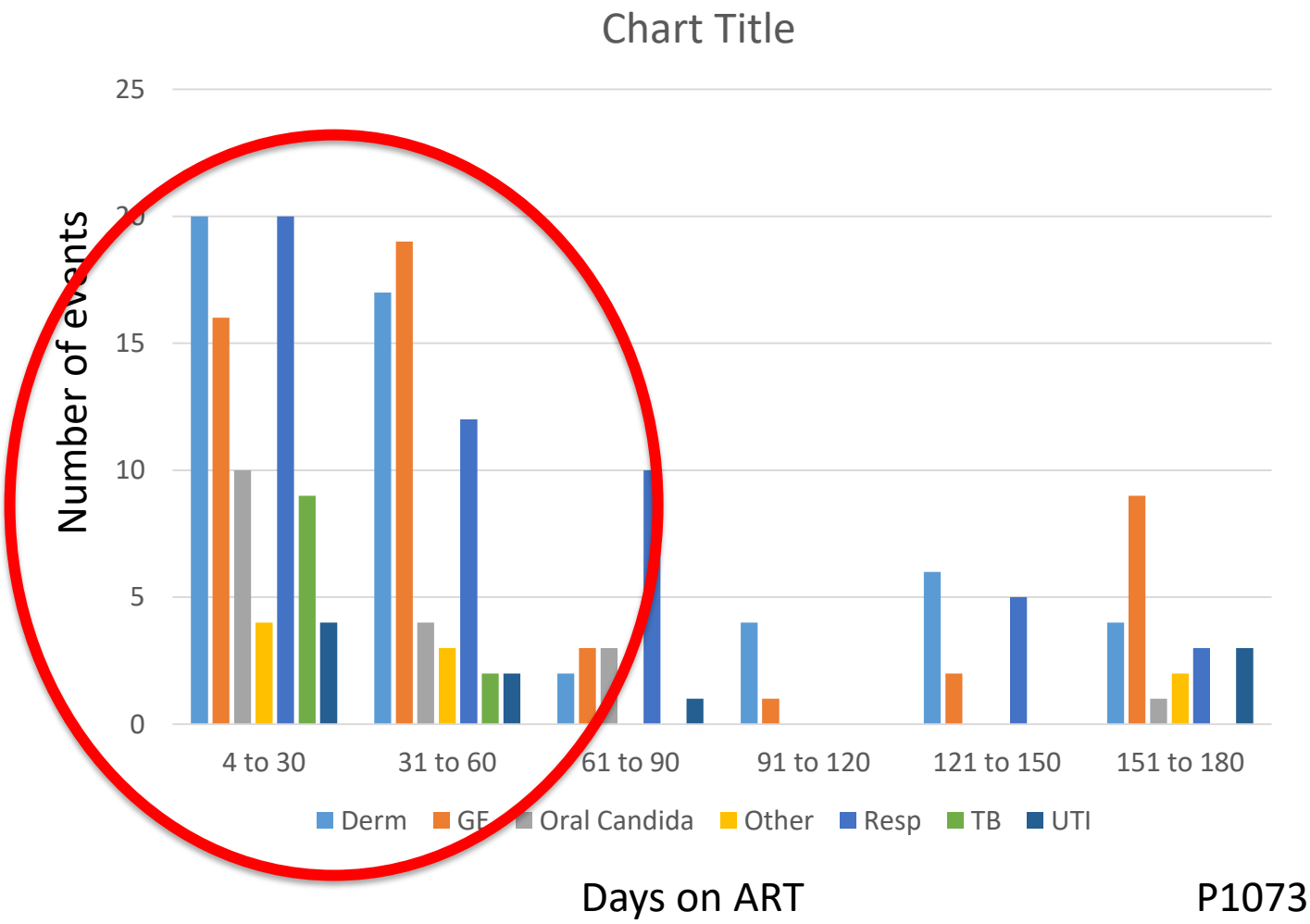
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Figure 2. Types of IRIS

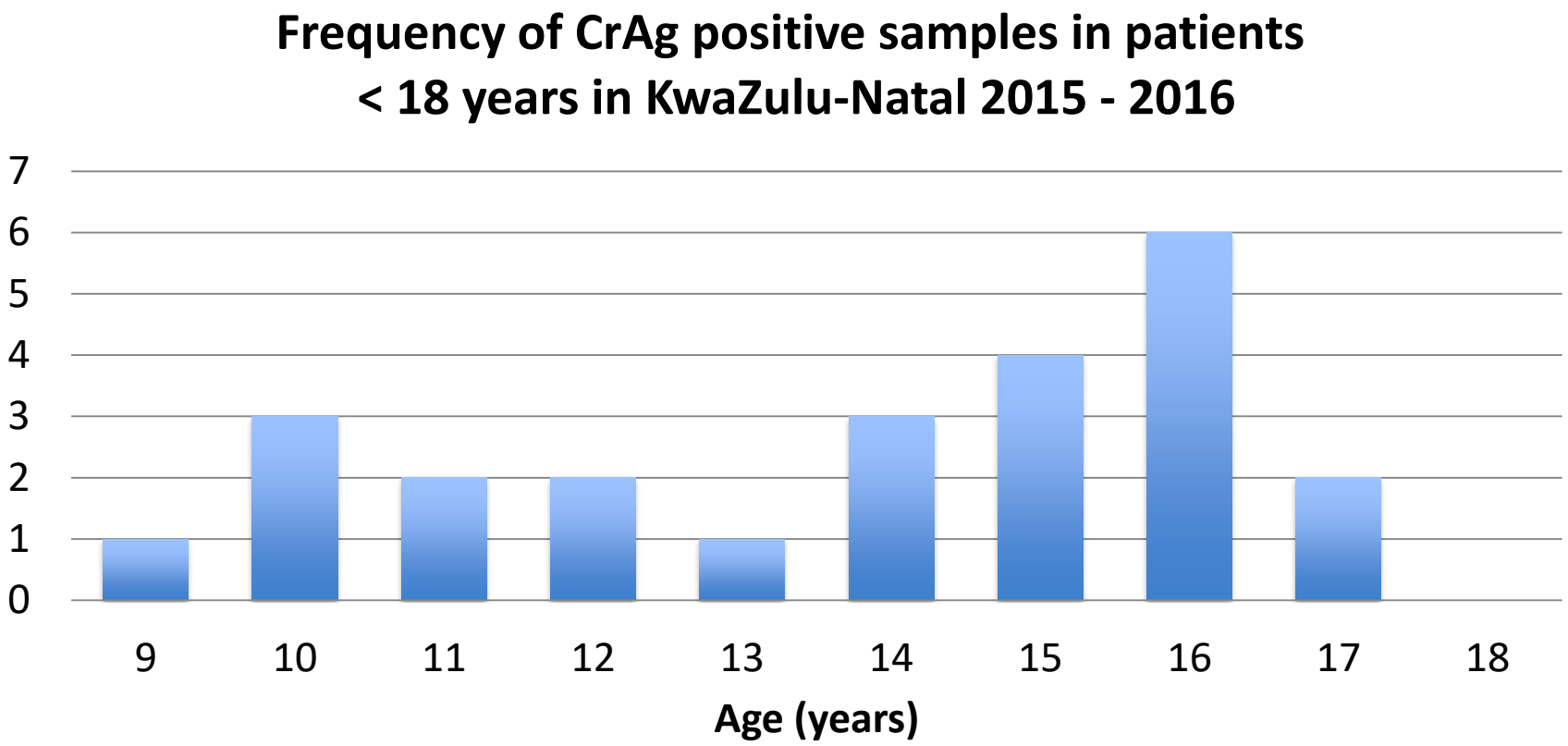


P1073

Supplementary figure 2. Non-IRIS infectious and inflammatory events



Cryptococcal Disease



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

Slide Courtesy of Moherdran 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 children[2]
- ARROW[3]: 7 / 1200 (all > than7 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

1. Hassan H, Cotton MF, Rabie H. Complicated and Protracted Cryptococcal Disease in HIV-infected Children. Pediatr Infect Dis J 2015;34:62–65
2. Meiring ST, Quan VC, Cohen C, et al. A comparison of pediatric- and adult onset cryptococcosis detected through population surveillance in South Africa, 2005–2007. AIDS. 2012;26:2307–2314
3. ARROW Trial team. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. doi:10.1016/S0140-6736(12)62198-9.

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

Le Roux et al PIDJ 2011

TABLE 1. Incidence Rates* of Death and Bacteremia by cART Exposure Time and TMP-SMX Prophylaxis Regimen

		Deaths				Bacteremias			
	Person Time (Person Years)	n	Incidence Rate (per 100 person years)	Incidence Rate Ratio (95% CI)	$P^{\dagger}$	n	Incidence Rate (per 100 person years)	Incidence Rate Ratio (95% CI)	$P^{\dagger}$
cART exposure									
Not on cART	306.3	41	13.4	Ref		26	8.5	Ref	—
≤3 mo on cART	43.2	4	9.3	0.69 (0.18–1.90)	0.25	14	32.4	**3.82 (1.84–7.58)**	**0.0002**
>3 mo on cART	321.9	8	2.4	**0.19 (0.08–0.40)**	**<0.0001**	7	2.2	**0.26 (0.09–0.61)**	**0.0005**
TMP-SMX prophylaxis									
Daily	318.31	29	6.80	Ref		13	4.08	Ref	
Thrice weekly	353.02	24	9.11	0.75 (0.41–1.33)	0.15	34	9.63	**2.36 (1.21–4.86)**	**0.006**
Total study	671.33	53	7.89			47	7.00	—	—

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."

$^{\dagger}P$ 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 × 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

Archary M et al. Bacterial infections in HIV-infected children admitted with severe acute malnutrition in Durban, South Africa. Paedaitric Int Child Health. Vol 37. Iss 1 2017

Other things to consider

- CMV – Ganciclovir
- Viral pneumonia and ventilatory support
- Diarrhoea – Fluid /ORS
- Dermatological conditions
- Growth monitoring and regular follow up


LAMIVUDINE 10 mg in 1mL Oral Soln
2ML BD
30 mL
DIRECTIONS ON MEDICINE CHART
KEEP OUT OF THE REACH OF CHILDREN
ABACAVIR 20 mg in 1mL Soln
6ml bd
85 mL
DIRECTIONS ON MEDICINE CHART
KEEP OUT OF THE REACH OF CHILDREN
Kaletra®
lopinavir/ritonavir
Oral Solution
Orale Oplossing
60 ml
ILVITRIM SUSPENSION
100 ml
SUSPENSION/SUSPENSIE
ZITHROMAX
200 mg / 5 ml
Pfizer
Winthrop Isoniazid
Isoniazid 100 mg
Isoniasied 100 mg
84 Tablets/84 Tablette
Wormstop® 100
100 mg
6 vernietig ingewande wurms
FLUCONAZOLE (FREE)
5mL Suspension
1 x 35 mL
DIRECTIONS ON MEDICINE
320254/TMAINP/11502
160901898
VITAMIN B6
PYRIDOXINE HCl
100 TABLETS

Pill Burden

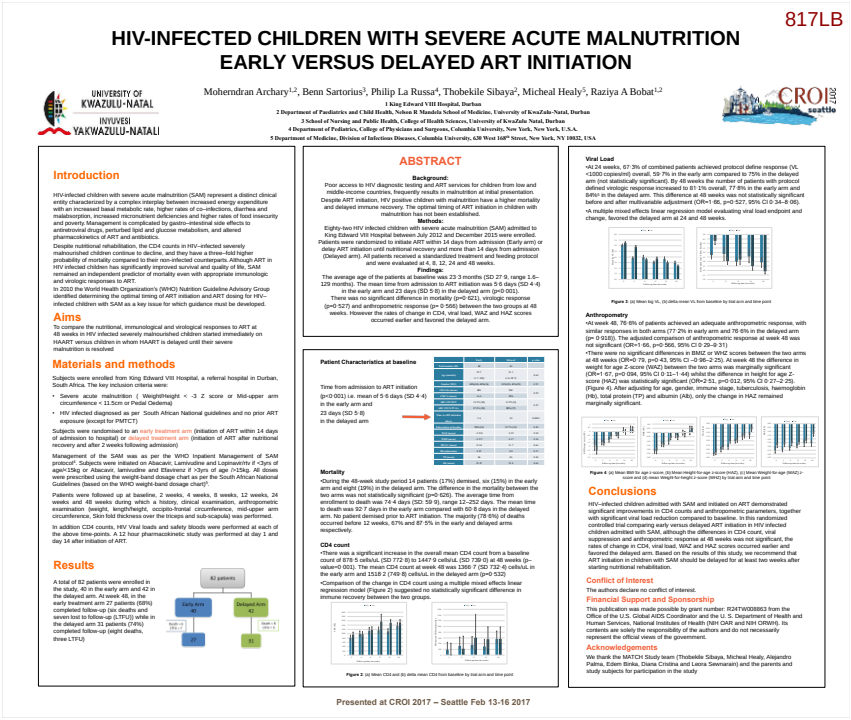

37 PAED WD
LAMIVUDINE 10 mg
30 mL
37 PAED WD
ABACAVIR 20 mg in 1
6ml bd
S4 Reg. No. 35/
Kaletra
lopinavir/ritor
Oral Solution
Orale Oplossing
60 ml
Lift label for further information and to indicate date of dispensing.
37 PAED WD
FLUCONAZOLE (FRED
5mL Susp
Qty: 1 x 35 mL
DIRECTIONS ON ME
320254/TMAINP/11502
160901898
Tygerberg
KEEP OU OF THE R
25 mg
VITAMIN B6
PYRIDOXINE HCl
100 TABLETS
PORTFOLIO
S4 Reg. No./Regnr.: 27/20.1.1/279
ZITHRO
AZITHRO
200 mg / 5 ml
03/2017
15 ml Powder for Oral Suspension
Poeier vir Mondelikse Suspensie
A17 (Act 101/1965)
SANOFI
nthrop Isoniazid 100
ILVITRIM
SUSPENSION
100 ml
Wormstop 100
6 vernietig ingewande wurms
Elke tablet bevat: Mebendasool
DOSIS: Voorbeeld vir verwysing
HOU BUITE BEREIK VAN KINDERS

How it could look ?

INH Cotrimoxazole B6

AZT/ABC 3TC Kaletra

When to start ART in children with Severe Acute Malnutrition



817LB

HIV-INFECTED CHILDREN WITH SEVERE ACUTE MALNUTRITION
EARLY VERSUS DELAYED ART INITIATION

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ABSTRACT

Background:
Poor access to HIV diagnostic testing and ART services for children from low and middle-income countries, frequently results in malnutrition at initial presentation. Despite ART initiation, HIV positive children with malnutrition have a higher mortality and delayed immune recovery. The optimal timing of ART initiation in children with malnutrition has not been established.

Methods:
Eighty-two HIV infected children with severe acute malnutrition (SAM) admitted to King Edward VIII Hospital between July 2012 and December 2015 were enrolled. Patients were randomized to initiate ART within 14 days from admission (Early arm) or delay ART initiation until nutritional recovery and more than 14 days from admission (Delayed arm). All patients received a standardized treatment and feeding protocol and were evaluated at 4, 8, 12, 24 and 48 weeks.

Findings:
The average age of the patients at baseline was 23 3 months (SD 27 9, range 1.6–129 months). The mean time from admission to ART initiation was 5 6 days (SD 4 4) in the early arm and 23 days (SD 5 8) in the delayed arm (p<0.001).
There was no significant difference in mortality (p=0 621), virologic response (p=0 527) and anthropometric response (p= 0 568) between the two groups at 48 weeks. However the rates of change in CD4, viral load, WAZ and HAZ scores occurred earlier and favored the delayed arm.

Introduction

HIV-infected children with severe acute malnutrition (SAM) represent a distinct clinical entity characterized by a complex interplay between increased energy expenditure with an increased basal metabolic rate, higher rates of co–infections, diarrhea and malabsorption, increased micronutrient deficiencies and higher rates of food insecurity and poverty. Management is complicated by gastro–intestinal side effects to antiretroviral drugs, perturbed lipid and glucose metabolism, and altered pharmacokinetics of ART and antibiotics.

Despite nutritional rehabilitation, the CD4 counts in HIV–infected severely malnourished children continue to decline, and they have a three–fold higher probability of mortality compared to their non-infected counterparts. Although ART in HIV infected children has significantly improved survival and quality of life, SAM remained an independent predictor of mortality even with appropriate immunologic and virologic responses to ART.

In 2010 the World Health Organization's (WHO) Nutrition Guideline Advisory Group identified determining the optimal timing of ART initiation and ART dosing for HIV–infected children with SAM as a key issue for which guidance must be developed.

Aims

To compare the nutritional, immunological and virological responses to ART at 48 weeks in HIV infected severely malnourished children started immediately on HAART versus children in whom HAART is delayed until their severe malnutrition is resolved

Materials and methods

Subjects were enrolled from King Edward VIII Hospital, a referral hospital in Durban, South Africa. The key inclusion criteria were:

- Severe acute malnutrition (Weight/Height < -3 Z score or Mid-upper arm circumference < 11.5cm or Pedal Oedema)
- HIV infected diagnosed as per South African National guidelines and no prior ART exposure (except for PMTCT)

Subjects were randomised to an early treatment arm (initiation of ART within 14 days of admission to hospital) or delayed treatment arm (initiation of ART after nutritional recovery and after 2 weeks following admission)

Management of the SAM was as per the WHO Inpatient Management of SAM protocol[4]. Subjects were initiated on Abacavir, Lamivudine and Lopinavir/r if <3yrs of age/<15kg or Abacavir, lamivudine and Efavirenz if >3yrs of age />15kg. All doses were prescribed using the weight-band dosage chart as per the South African National Guidelines (based on the WHO weight-band dosage chart)[5].

Patients were followed up at baseline, 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks and 48 weeks during which a history, clinical examination, anthropometric examination (weight, length/height, occipito-frontal circumference, mid-upper arm circumference, Skin fold thickness over the triceps and sub-scapula) was performed.

In addition CD4 counts, HIV Viral loads and safety bloods were performed at each of the above time-points. A 12 hour pharmacokinetic study was performed at day 1 and day 14 after initiation of ART.

Results

A total of 82 patients were enrolled in the study, 40 in the early arm and 42 in the delayed arm. At week 48, in the early treatment arm 27 patients (68%) completed follow-up (six deaths and seven lost to follow-up (LTFU)) while in the delayed arm 31 patients (74%) completed follow-up (eight deaths, three LTFU)

Patient Characteristics at baseline

Time from admission to ART initiation (p<0 001) i.e. mean of 5 6 days (SD 4 4) in the early arm and 23 days (SD 5 8) in the delayed arm

Mortality

•During the 48-week study period 14 patients (17%) demised, six (15%) in the early arm and eight (19%) in the delayed arm. The difference in the mortality between the two arms was not statistically significant (p=0 626). The average time from enrollment to death was 74 4 days (SD 59 0), range 12–252 days. The mean time to death was 92 7 days in the early arm compared with 60 8 days in the delayed arm. No patient demised prior to ART initiation. The majority (78 6%) of deaths occurred before 12 weeks, 67% and 87 5% in the early and delayed arms respectively.

CD4 count

•There was a significant increase in the overall mean CD4 count from a baseline count of 878 5 cells/uL (SD 772 8) to 1447 9 cells/uL (SD 738 0) at 48 weeks (p–value=0 001). The mean CD4 count at week 48 was 1366 7 (SD 732 4) cells/uL in the early arm and 1518 2 (749 8) cells/uL in the delayed arm (p=0 532)

•Comparison of the change in CD4 count using a multiple mixed effects linear regression model (Figure 2) suggested no statistically significant difference in immune recovery between the two groups.

Viral Load

•At 24 weeks, 67 3% of combined patients achieved protocol define response (VL <1000 copies/ml) overall, 59 7% in the early arm compared to 75% in the delayed arm (not statistically significant). By 48 weeks the number of patients with protocol defined virologic response increased to 81 1% overall, 77 8% in the early arm and 84%! in the delayed arm. This difference at 48 weeks was not statistically significant before and after multivariable adjustment (OR=1 66, p=0 527, 95% CI 0 34–8 08).

•A multiple mixed effects linear regression model evaluating viral load endpoint and change, favored the delayed arm at 24 and 48 weeks.

Anthropometry

•At week 48, 76 6% of patients achieved an adequate anthropometric response, with similar responses in both arms (77 2% in early arm and 76 6% in the delayed arm (p= 0 918). The adjusted comparison of anthropometric response at week 48 was not significant (OR=1 66, p=0 566, 95% CI 0 29–9 31)

•There were no significant differences in BMIZ or WHZ scores between the two arms at 48 weeks (OR=0 79, p=0 43, 95% CI –0 98–2 25). At week 48 the difference in weight for age Z-score (WAZ) between the two arms was marginally significant (OR=1 67, p=0 094, 95% CI 0 11–1 44) whilst the difference in height for age Z-score (HAZ) was statistically significant (OR=2 51, p=0 012, 95% CI 0 21–2 25). (Figure 4). After adjusting for age, gender, immune stage, tuberculosis, haemoglobin (Hb), total protein (TP) and albumin (Alb), only the change in HAZ remained marginally significant.

Conclusions

HIV–infected children admitted with SAM and initiated on ART demonstrated significant improvements in CD4 counts and anthropometric parameters, together with significant viral load reduction compared to baseline. In this randomized controlled trial comparing early versus delayed ART initiation in HIV infected children admitted with SAM, although the differences in CD4 count, viral suppression and anthropometric response at 48 weeks was not significant, the rates of change in CD4, viral load, WAZ and HAZ scores occurred earlier and favored the delayed arm. Based on the results of this study, we recommend that ART initiation in children with SAM should be delayed for at least two weeks after starting nutritional rehabilitation.

Conflict of Interest
The authors declare no conflict of interest.

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- Average age 23.3 months
- Mean time from admission to ART start:
  - Early 5.6 d (SD4.4)
  - 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

Urgent Versus Post-Stabilization ART in Hospitalized Children: A Randomized Trial

- 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).

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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
Diagnosis	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 Or at any CD4 count if seriously ill	Yes	Yes	Yes[a]
	Cryptococcal antigen screening	≤100 cells/mm³	Yes	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis[b]	≤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 For criteria, see Annex 1
	TB preventive treatment[b]	Any	Yes	Yes	Yes[c]
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm³	Yes	Yes	Not applicable (screening not advised)
ART initiation	Rapid ART initiation (as recommended in Chapter 3)	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest TB or cryptococcal meningitis (see Chapter 3)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm³	Yes	Yes	Yes

[a] Limited data available for children. [b] Co-trimoxazole, isoniazid and pyridoxine are available as a fixed-dose combination tablet.
[c] 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

Intervention	Indication to start			Indication to stop		
	Adults	Adolescents	Children	Adults	Adolescents	Children
Co-trimoxazole prophylaxis	Severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or with a CD4 cell count <350 cells/mm^3. *Strong recommendation, moderate-quality evidence* Malaria and/or severe bacterial infections highly prevalent: co-trimoxazole, prophylaxis should be initiated regardless of CD4 cell count or WHO stage. *Conditional recommendation, moderate-quality evidence*	Same as children	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/mm^3. *Strong recommendation, high-quality evidence*	Clinically stable on ART, with evidence of immune recovery and viral suppression. *Conditional recommendation, low-quality evidence* Malaria and /or severe bacterial infections are highly prevalent: co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage. *Conditional recommendation, moderate-quality evidence*	Same as children	High prevalence of malaria and/or severe bacterial infections: continued regardless of whether ART is provided. *Conditional recommendation, moderate-quality evidence* Low prevalence of malaria and/or severe bacterial infections: discontinued for children who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 cell count >350 cells/mm^3. *Strong recommendation, very-low-quality evidence*

Intervention	Indication to start			Indication to stop		
	Adults	Adolescents	Children	Adults	Adolescents	Children
TB preventive treatment	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. *Strong recommendation, moderate-quality evidence* 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. *Strong recommendation, high-quality evidence* 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. *Strong recommendation, moderate-quality evidence*	Same as adults	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. *Strong recommendation, low-quality evidence* 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. *Strong recommendation, low-quality evidence* 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. *Conditional recommendation, low-quality evidence* All children living with HIV, after successfully completing treatment for TB, should receive isoniazid preventive therapy for an additional 6 months. *Conditional recommendation, low-quality evidence*	After six or at least 36 months according to the recommendation adopted	After six or at least 36 months according to the recommendation adopted	After six months

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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.