Current challenges of paediatric HIV care – Experiences in Sub-Saharan Africa

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Current Challenges of Paediatric HIV Care – What is Happening in the Countries?

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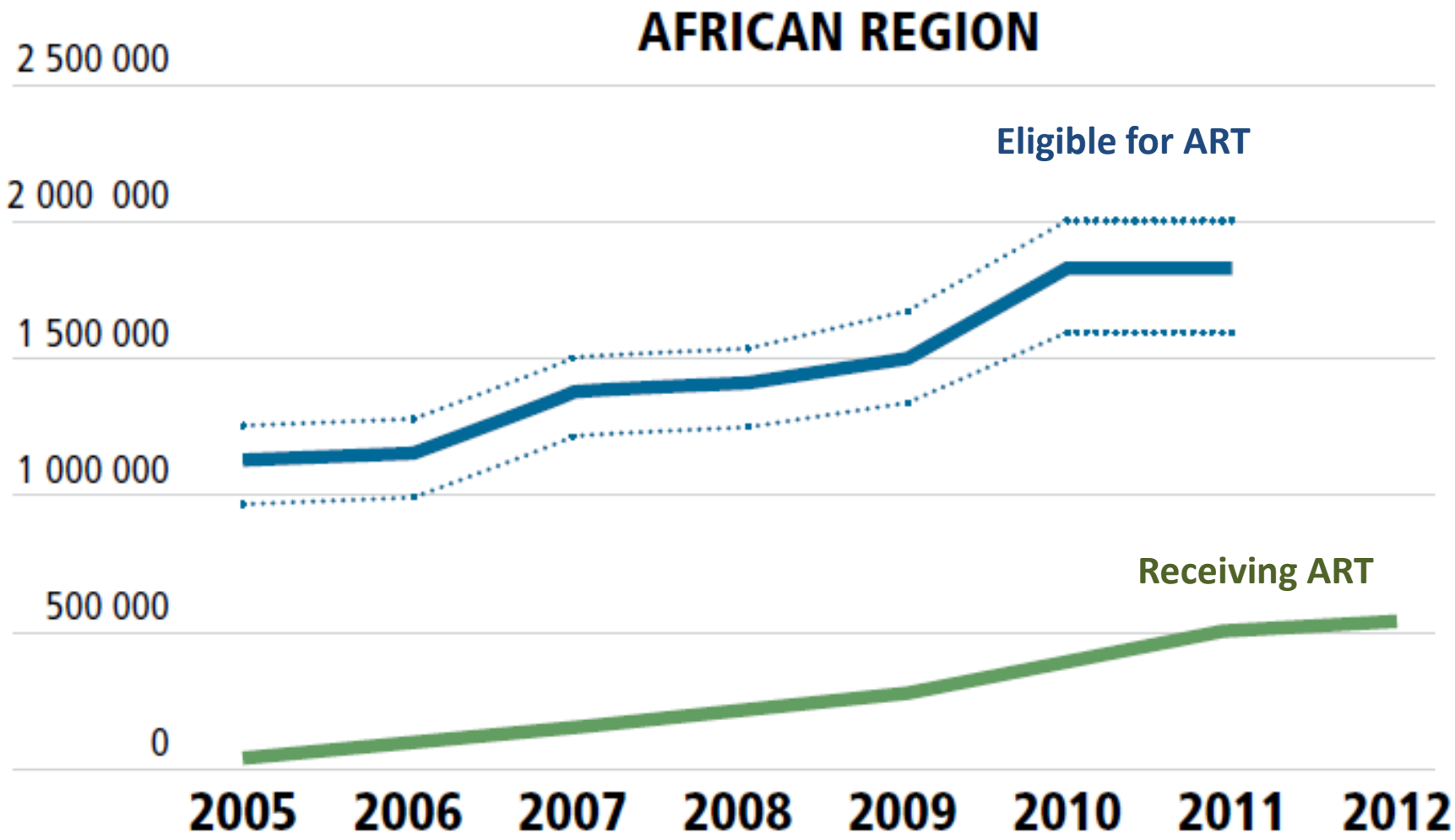
Presentation includes discussion of the off-label use of a drug or drugs

Outline

- Linkage of newly diagnosed HIV+ children to long-term HIV care
- Late presentation of most children in advanced HIV disease
- Late detection of ART failure using current monitoring approaches
- High TB – HIV co-infection and drug interaction challenges for children < 3yr.
- Limited paediatric ARV formulations, and limited options for children failing PI regimens

LINKAGE OF NEWLY DIAGNOSED HIV INFECTED CHILDREN TO CARE

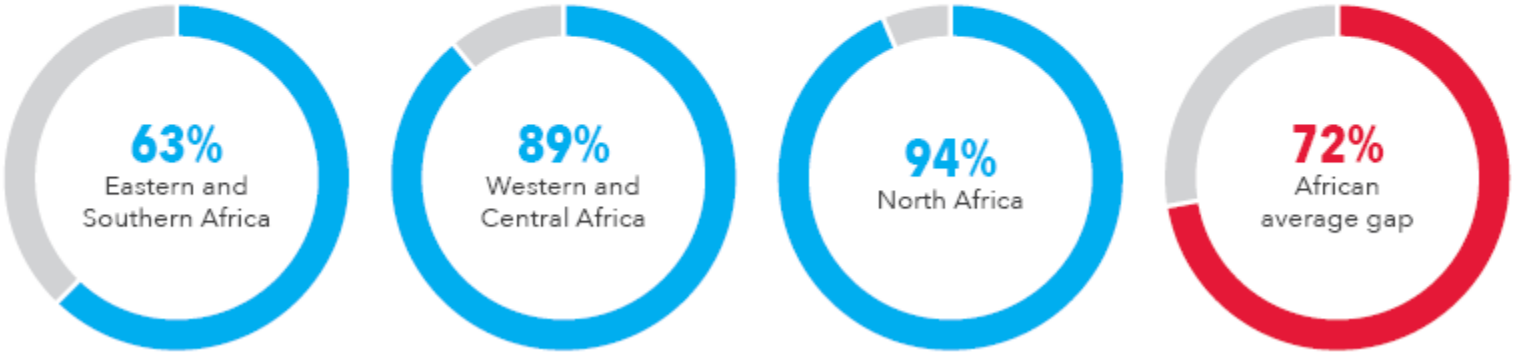
Children (0–14 yr old) eligible for ART (2005–2011) and receiving it (2005–2012)



2013 Global AIDS Response Reporting (WHO/UNICEF/UNAIDS) and 2012 UNAIDS/WHO estimates

Sub Saharan Africa Gap in ART for Children

FIG. 4
Regional gaps in antiretroviral therapy for children (0-14 years), 2012 - 2013



Why are 72% of eligible African HIV infected children not on ART?

- ✧ They do not yet know their diagnosis
- ✧ When diagnosed, poor linkage to long-term care
- ✧ Even after starting ART, high drop off due various factors

UNAIDS 2012 Estimates

HIV+ Children Present to Care Late in SS Africa

Patient characteristics	Kenya Natl. Survey	S. African 5 sites 4 countries*
Number of children	7,332	8,225
Female %	51.2%	49.4%
Median age, years (IQR)	2.6 (1.1-6.4)	4.0 (1.5-7.7)yr
HIV WHO Stage III/IV	**45.6%**	**78.4%**
Median baseline CD4% (IQR)	**16 (10 -24)%**	**11.6 (7-17)%**
Median follow-up time, yrs (IQR)	2.4 (0.6, 4.2)	1.4 (0.6-2.5)yr
Proportion Deaths	7.3%	4.5%**
Died in 1st 3 mth ART	-	**273/391 (70%)**

* Malawi, Cape Town, Johannesburg, Zimbabwe, Mozambique
** Unadjusted
Kenya National Paed Survey 2004 – 2010 (LSPCTIK), IeDEA-SA, Fenner L, JAIDS 2010

LATE DETECTION OF ART FAILURE USING CURRENT MONITORING APPROACHES

Clinical/Immunologic Criteria Inadequate for Detecting & Confirming ART failure

Country	Cohort size	Sensitivity (%)	Specificity (%)	Positive Predictive value (%)	Negative Predictive Value (%)
Rakai, Uganda[a] 2009	1133	28	90	8	97
Nigeria (4 sites)[b] 2011	9690	58	75	39	87

- CD4 has low sensitivity and positive predictive value (PPV) to detect virologic ART failure
- Targeted VL in children with WHO defined clinical/immunologic failure increased the PPV of WHO criteria from **49% to 82%** (South Africa)[c]**.**
- WHO 2013 guideline now recommends routine VL monitoring
- But: access extremely limited in SS Africa due to cost.

[a]HE Rawizza et al, CID 2011. [b]SJ Reynolds et al, AIDS 2009.
[c]IeDEA-SA, Mary-Ann Davies, Trop Med Int Health 2012

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Long-term Virologic Response and Genotypic Resistance Mutations in HIV-1 Infected Kenyan Children on Combination Antiretroviral Therapy

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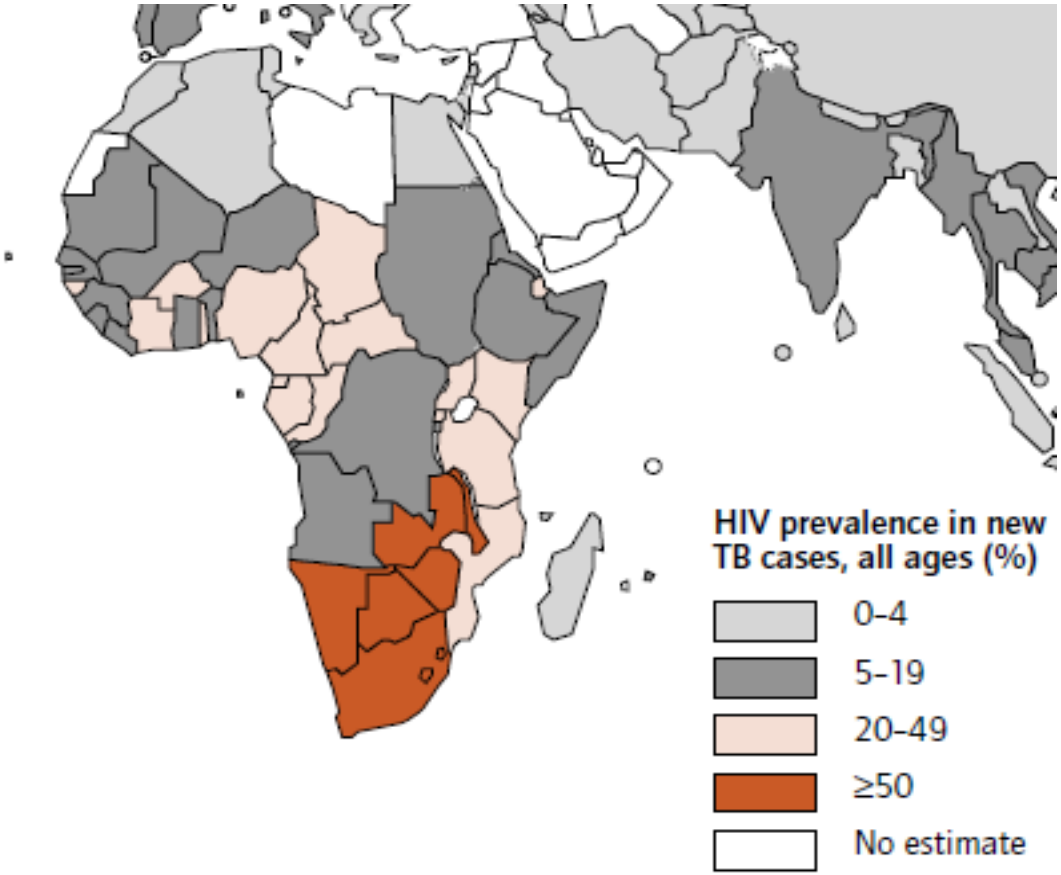
The implications of delay in detecting virologic failure are illustrated in this cohort

High TB – HIV co-infection and drug interaction challenges for children < 3yr.

High TB – HIV Co-infection in SS Africa



HIV Prevalence in All TB cases (WHO 2007)

Southern Africa: > 50%
Eastern Africa: 20 – 49%
Central Africa: 5 – 19%
West Africa: 5 – 49%
SS Africa: 43%
(UNAIDS 2013)

In Children, HIV prevalence

Kenya National 2007: 38%
S. Africa (CT, 2007): 32%
Ethiopia 2009: 5%

Global TB Control 2009.
Kenya National TB Program 2007. Schaaf S et al, 2007, Ramos JM et al 2010

In Children TB Kills; Necropsy Evidence Zambia

	Total*	Adjusted % (SE)†	HIV-positive (n=180)	HIV-negative (n=84)	Odds ratio (95%CI)	p
Diagnosis						
Acute pyogenic pneumonia	116 (44%)	39·1% (3·2)	74 (41%)	42 (50%)	0·70 (0·40–1·21)	0·22
PCP	58 (22%)	27·5 % (3·1)	52 (29%)	6 (7%)	5·28 (2·12–15·68)	0·0001
Tuberculosis	54 (20%)	18·8% (2·5)	32 (18%)	22 (26%)	0·61 (0·31–1·18)	0·16
CMV	43 (16%)	20·2% (2·8)	40 (22%)	3 (4%)	7·71 (2·33–40·0)	0·0002
Interstitial pneumonitis	30 (11%)	11·8% (2·1)	15 (8%)	15 (18%)	0·42 (0·18–0·96)	0·04
Shock lung	27 (10%)	11·5% (2·2)	24 (13%)	3 (4%)	4·15 (1·20–22·10)	0·03
Pulmonary oedema	19 (7%)	6·4% (1·6)	10 (6%)	9 (11%)	0·49 (0·18–1·38)	0·21
Lymphocytic interstitial pneumonitis	10 (4%)	3·8% (1·2)	9 (5%)	1 (1%)	4·37 (0·59–193·7)	0·21

PCP=*Pneumocystis carinii* pneumonia. *Fewer than ten cases were noted of: measles (five HIV-1-positive, two HIV-1-negative), pleurisy (five HIV-1-positive), pulmonary embolism (one HIV-1-negative), respiratory syncytial virus pneumonia (one HIV-1-positive, one HIV-1-negative), herpes simplex virus pneumonia (one HIV-1-positive), lipoidal pneumonia (one HIV-1-positive), malaria (two HIV-1-negative), normal lung (one HIV-1-positive, two HIV-1-negative), Kaposi's sarcoma (two HIV-1-positive), bronchiolitis (three HIV-1-positive). †Percentages and standard errors adjusted to show age/sex structure of all deaths from respiratory disease during the study period.

Table 1: **Lung diseases identified at necropsy, by HIV-1 status**

Autopsies on 264 children who died from respiratory disease.

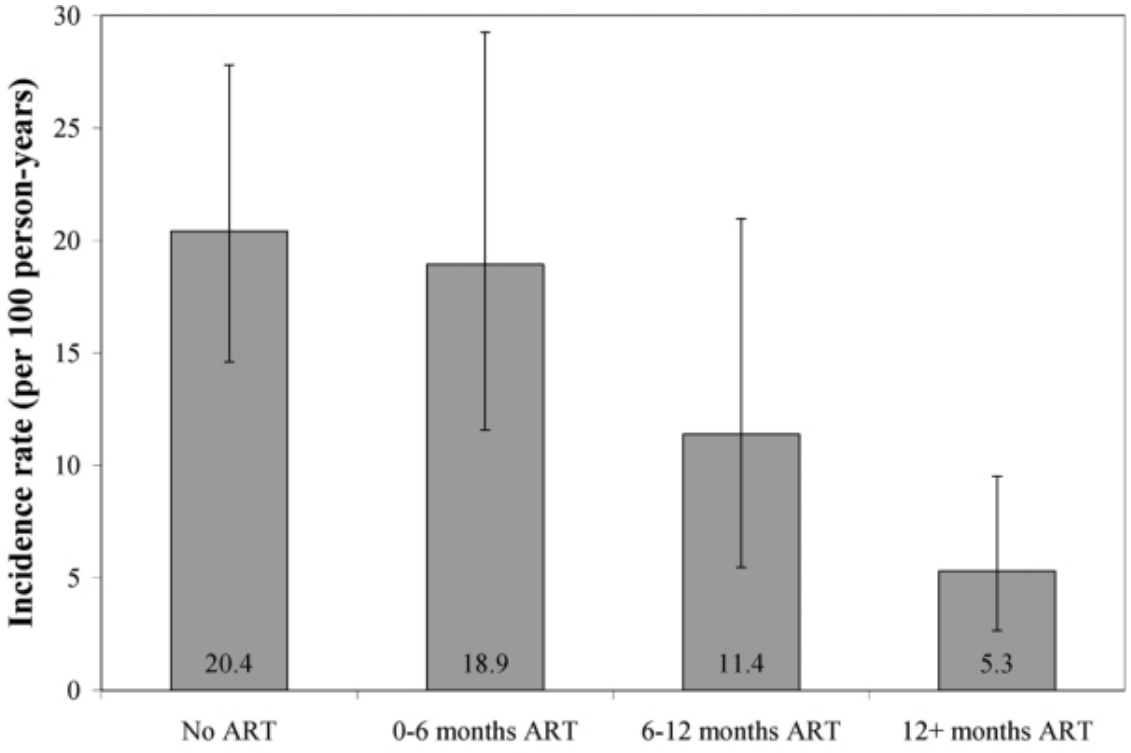
Age 0 – 15yr, median age 8mth. **Top causes of pneumonia death:**

HIV positive: Pyogenic pneumonia, PCP, **TB,** CMV

HIV negative: Pyogenic pneumonia, TB, viral (interstitial pneumonitis)

Chintu C et al, Lancet 2002

ART reduces incidence of TB **5 fold** in HIV infected Children (DR Congo)



Number of TB events:	40	20	10	11
Person-years:	195.9	105.6	87.7	206.9
Incidence rate per 100 person years:	20.4	18.9	11.4	5.3
(95% CI):	(14.6–27.8)	(11.6–29.3)	(5.5–21.0)	(2.7–9.5)

Edmonds A et al, Int J Epidem 2009.

Concurrent ART with Anti-TB Treatment Poses Many Challenges In Children

Rifampicin – Backbone of TB Rx – induces metabolism of several key ARV drugs:

- Reduces NVP levels by 10-68%
  - Minimal effect on EFV
- Reduces Lopinavir levels by 80%
  - Double dosing LPV/r does not fix this
  - Super-boosting with Ritonavir fixes it, but unpalatable unstable liquid formulations limit feasibility in SSA
- Limited options for Rx child < 3yr
  - Triple NRTI (efficacy?) versus EFV (dose uncertain)
  - Then revert to 2 class drug regimen after TB Rx

Kwara A, Expert Opin Drug Metab Toxicol. 2010.
McIlleron H, Antivir Ther 2011, Frohoff C, PLOS1 2011. Ren Y, JAIDS 2008. ARROW trial, Lancet 2013

LIMITED PAEDIATRIC ARV FORMULATIONS
LIMITED OPTIONS FOR CHILDREN FAILING PROTEASE INHIBITOR BASED REGIMENS

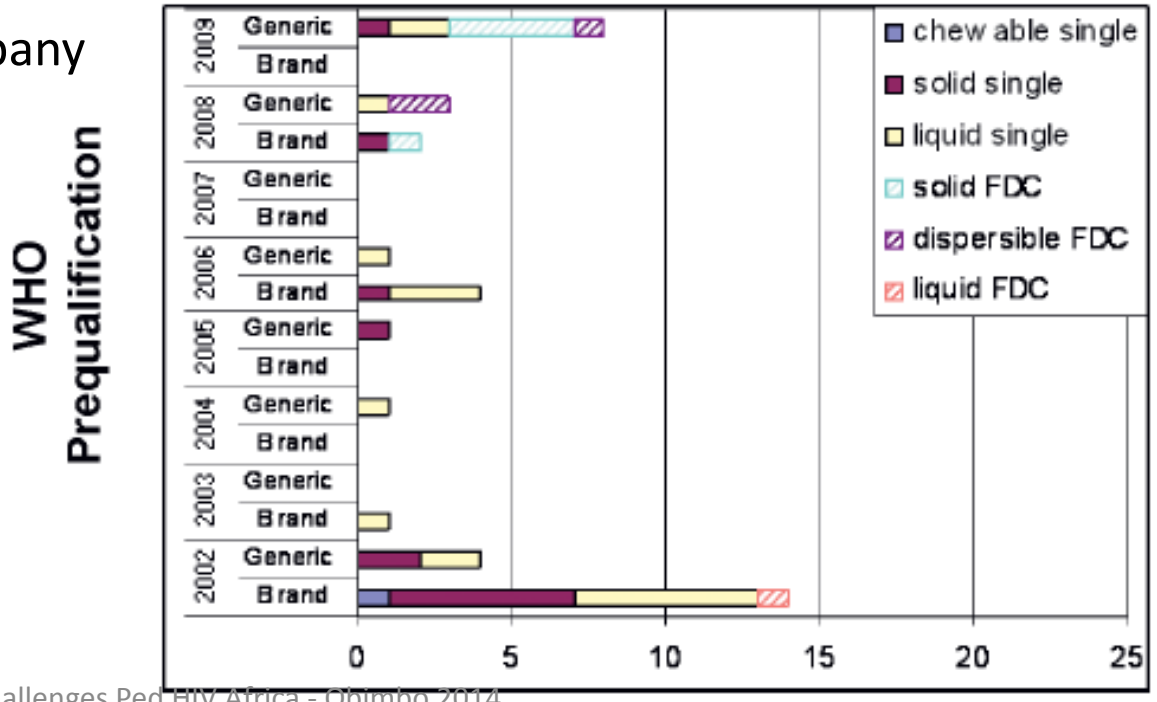
Limited Paediatric FDC Formulations

Shows all WHO Paed ARV approvals over period 2002 – 2009

- ✓Notable few FDCs formulations
- ✓Most FDCs are solid (light blue)
- ✓Few dispersible **(PURPLE)**
- ✓Most FDCs have single company manufacturer

Implication:

- ✓ Young children receive 3 separate ARV drugs
- ✓ Complex for parent to measure
- ✓ High pill/volume burden

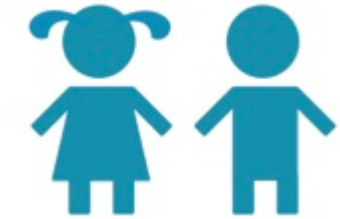


Waning et al. BMC Pediatrics 2010

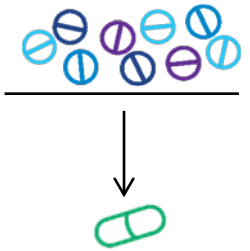
Current need for Paediatric HIV Care

New guidelines for paediatric HIV care issued by the World Health Organization in June 2013

Important special formulations for children living with HIV identified



Simpler treatment options, if possible in fixed-dose combinations needed



- ✧ Paediatric market is small
- ✧ Unattractive for companies to invest in new formulations
- ✧ This can compromise access

Medicine Patent Pool 2010

WHO Mid and Long-term Priorities

FORMULATIONS

- ABC/3TC/EFV
- ABC or AZT/3TC/LPVr
- RTV granules
- DRV/r co-formulated
- ATV/r in co-formulated

NEW AGENTS

- Dolutegravir
- TAF
- Cobicistat

		Age 0–3 years		Age 3–10 years	
		Option 1	Option 2	Option 1	Option 2
Medium-term	First line	ABC + 3TC + LPV/r	AZT + 3TC + LPV/r	Not applicable	Not applicable
	Second line	AZT + 3TC + DRV/r	ABC + 3TC + RAL[a]		
	Third line	Optimized background regimen + RAL	Optimized background regimen + DRV/r		
Long-term	First line	TAF + 3TC + DTG or ABC + 3TC + DTG			
	Second line	AZT + 3TC + LPV/r or ATV/r[b]			
	Third line	DRV/r[c] + ETR or EFV			

World Health Organization

Adapted from the recommendations of the Paediatric ARV Drug Optimization Conference, Dakar, Senegal, 22–23 October 2013.

Summary – Africa Challenges

- Children present with advanced HIV
- Challenges in linking all newly diagnosed children to long-term care
- Current monitoring approaches detect ART failure late
- TB – HIV co-infection is common and drug interaction challenges for children < 3yr.
- Limited paediatric ARV formulations, and limited options for children failing PI regimens