Developments in Paediatric ART Practice

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Overview

- Global state of paediatric ART
- Filling the gaps in paediatric ART cover
- Best practices in paediatric care:
  - Diagnosis
  - When to start
  - What to start
  - When to switch
  - What to switch to
  - How to maintain sustained adherence
  - What is new in paediatric ART

Global State of Paediatric ART

Celebrating successes/Acknowledging failures

Percentage Decrease Between 2009 and 2011 in the Number of Children (0–14 Years Old) Acquiring HIV Infection in Countries with Generalized Epidemics

Increased

Angola
Congo
Equatorial Guinea
Guinea-Bissau

1–19%

Benin
Burkina Faso
Central African Republic
Chad
Djibouti
Eritrea
Gabon
Mozambique
Nigeria
South Sudan
United Republic of Tanzania

20–39%

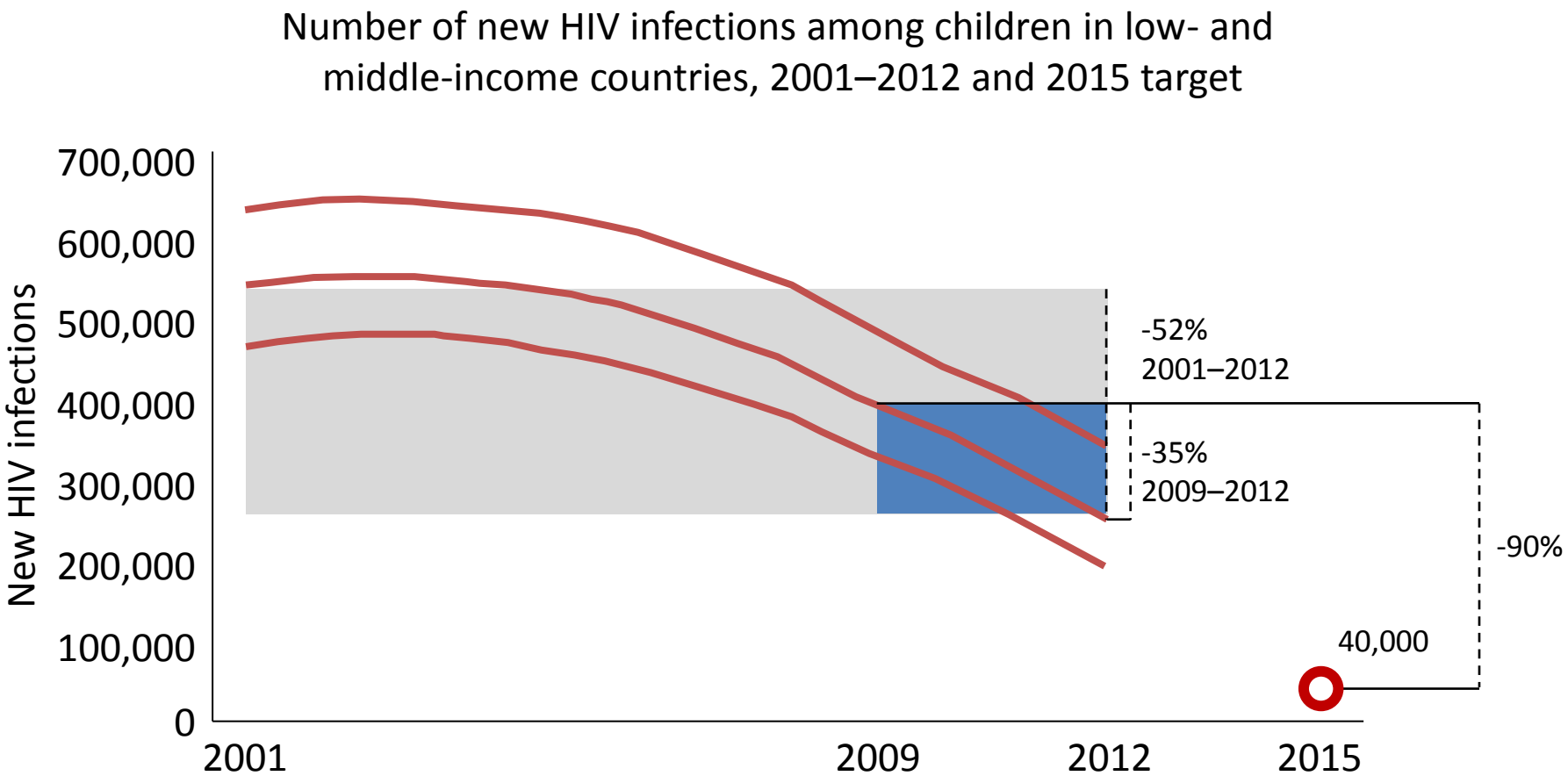
Botswana
Cameroon
Côte d'Ivoire
Ethiopia
Ghana
Guinea
Haiti
Lesotho
Liberia
Malawi
Papua New Guinea
Rwanda
Sierra Leone
Swaziland
Uganda
Zimbabwe

40–59%

Burundi
Kenya
Namibia
South Africa
Togo
Zambia

UNAIDS report on the global AIDS epidemic 2012. Available at:
http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_unaids_global_report_2012_with_annexes_en.pdf

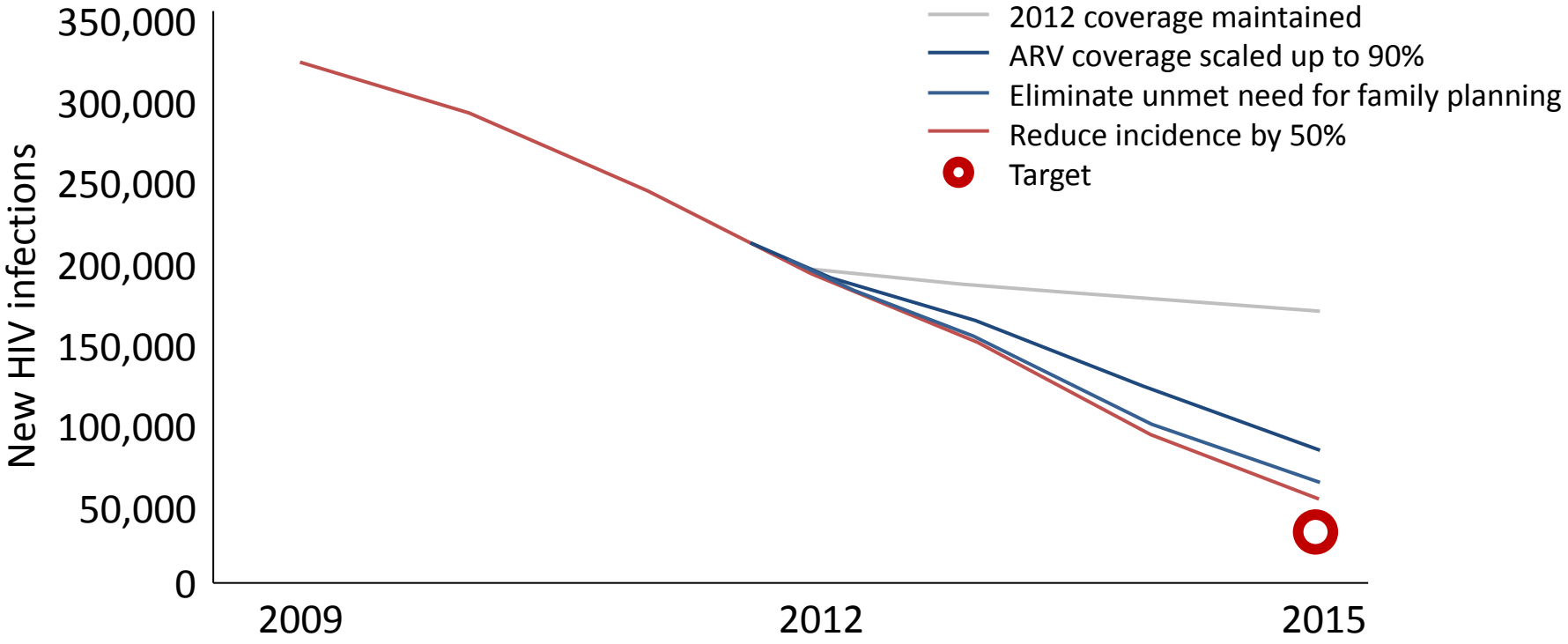
Global State of Paediatric ART



UNAIDS report on the global AIDS epidemic 2013. Available at:
http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf

Global State of Paediatric ART

Projected impact on new child HIV infections by programmes to prevent mother-to-child transmission, 21 Global Plan priority countries in sub-Saharan Africa, 2009–2015



UNAIDS report on the global AIDS epidemic 2013. Available at:
http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf

34%

COVERAGE FOR CHILDREN

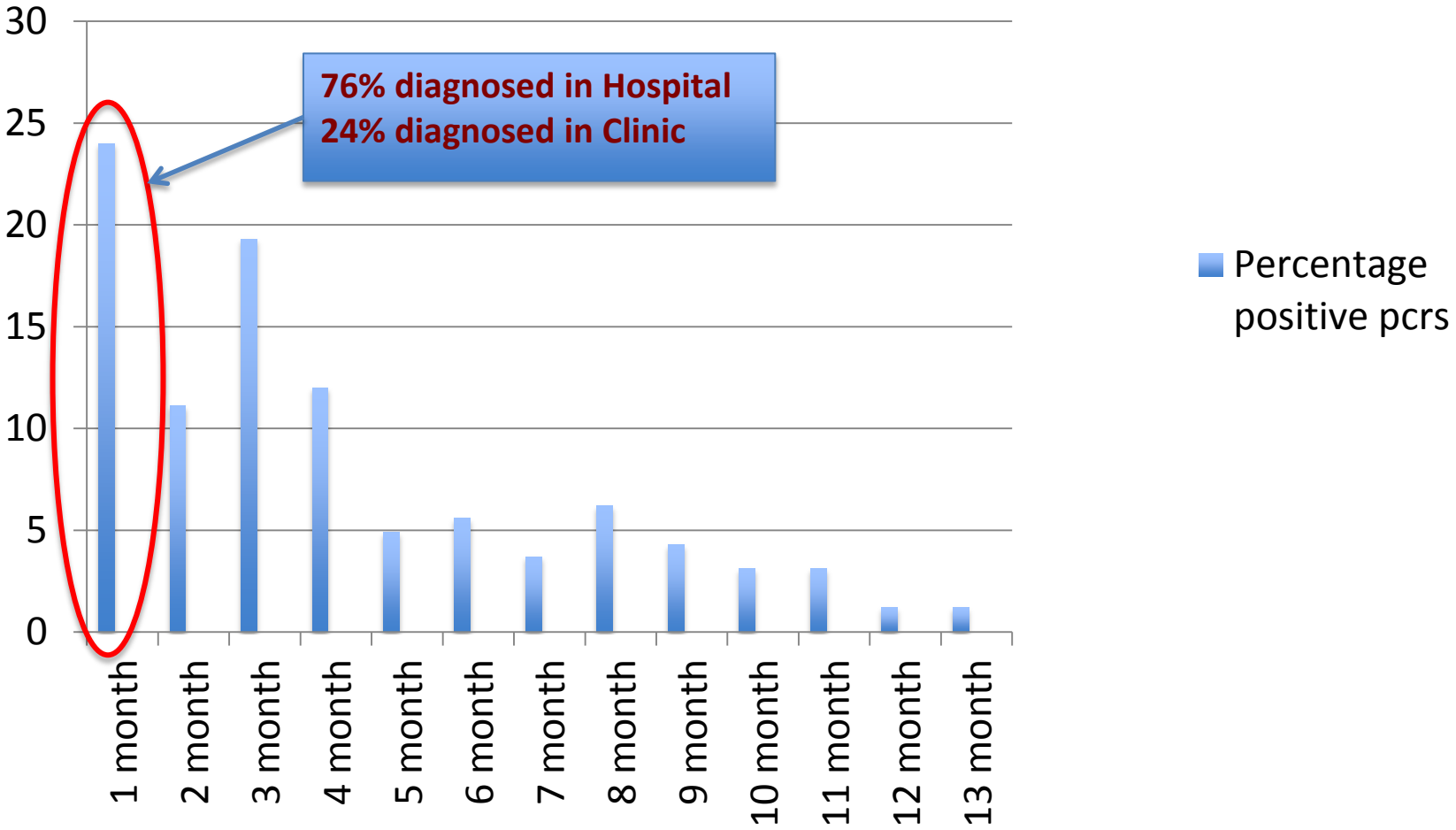
WHY THE DIFFERENCE ?

HIV treatment coverage is 61% for women and 47% for men in low- and middle-income countries, compared with 34% for children

WHO 2014 supplement. Available at: http://www.zero-hiv.org/wp-content/uploads/2014/03/Technical_Report_template_Topic5_27feb_FINAL_LR_WEB.pdf

3.4 Kg Baby – First Referral to Hospital

Positive DNA Pcr KZN – July 2014



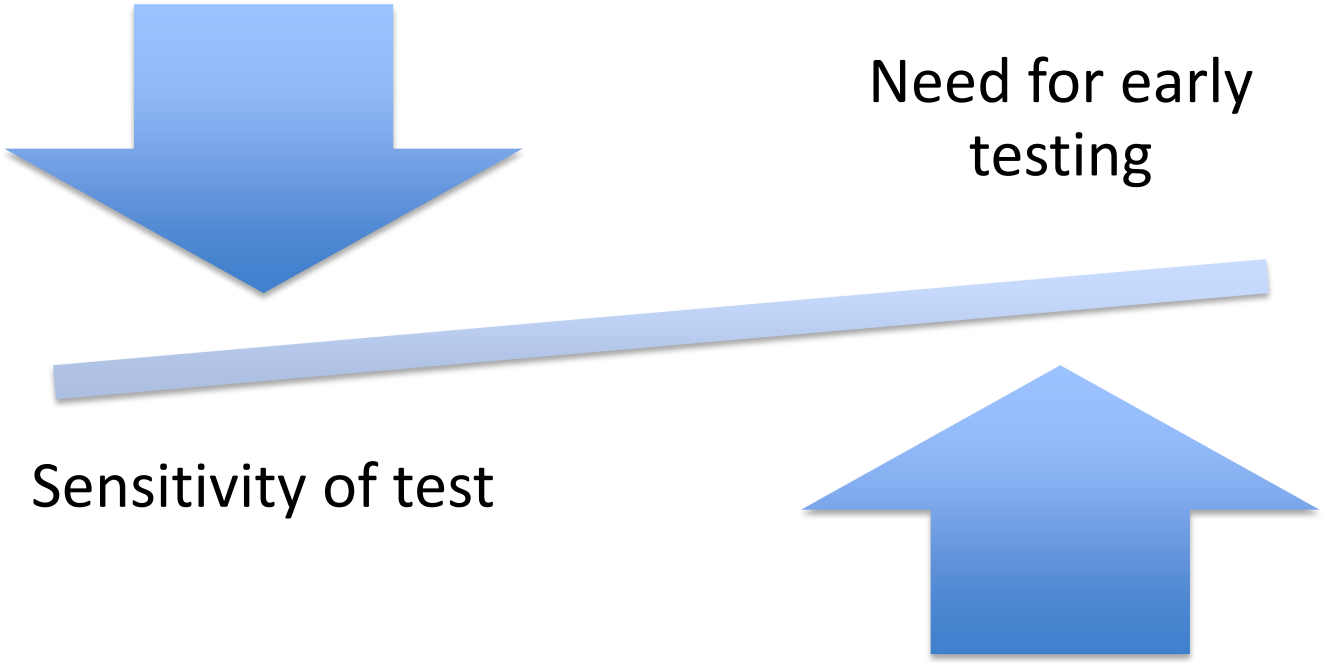
Key Barriers to Paediatric ART Initiation

- Individual level factors:[1]
  - Fear and stigma
  - Caregivers unawareness of HIV symptoms
  - Living without parents
  - Unemployment of the caregiver
  - Lack of perinatal prophylaxis
  - High transportation costs to the clinic
- Health system issues:
  - Failure to link perinatal, well baby care to paediatric ART care
  - Problems with diagnosis of paediatric HIV (especially <18 months)
  - Healthcare worker
    - Lack of identification of common HIV symptoms
    - Reluctance to start ART in children – perceived to be complicated

1. Boender TS, et al. AIDS Res Treat 2012;817506

Diagnosis

- Optimal timing of HIV testing in children is a balancing act

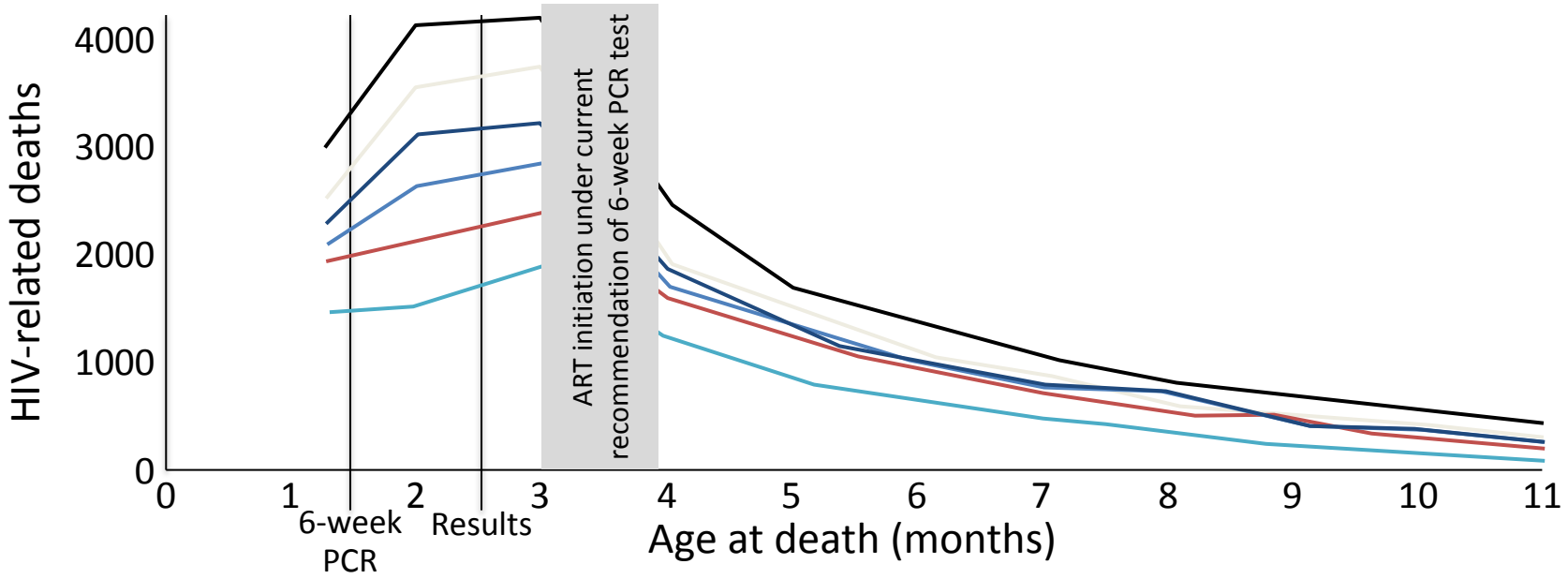


Virologic Testing and Mortality Rates in Neonates

Sensitivity and specificity of neonatal PCR

	Birth	2–4 weeks	3–6 months
Sensitivity	55%	90%	100%
Specificity	99.8%	100%	100%

Peak of mortality in South Africa & timing of virological testing & early treatment in different cohorts



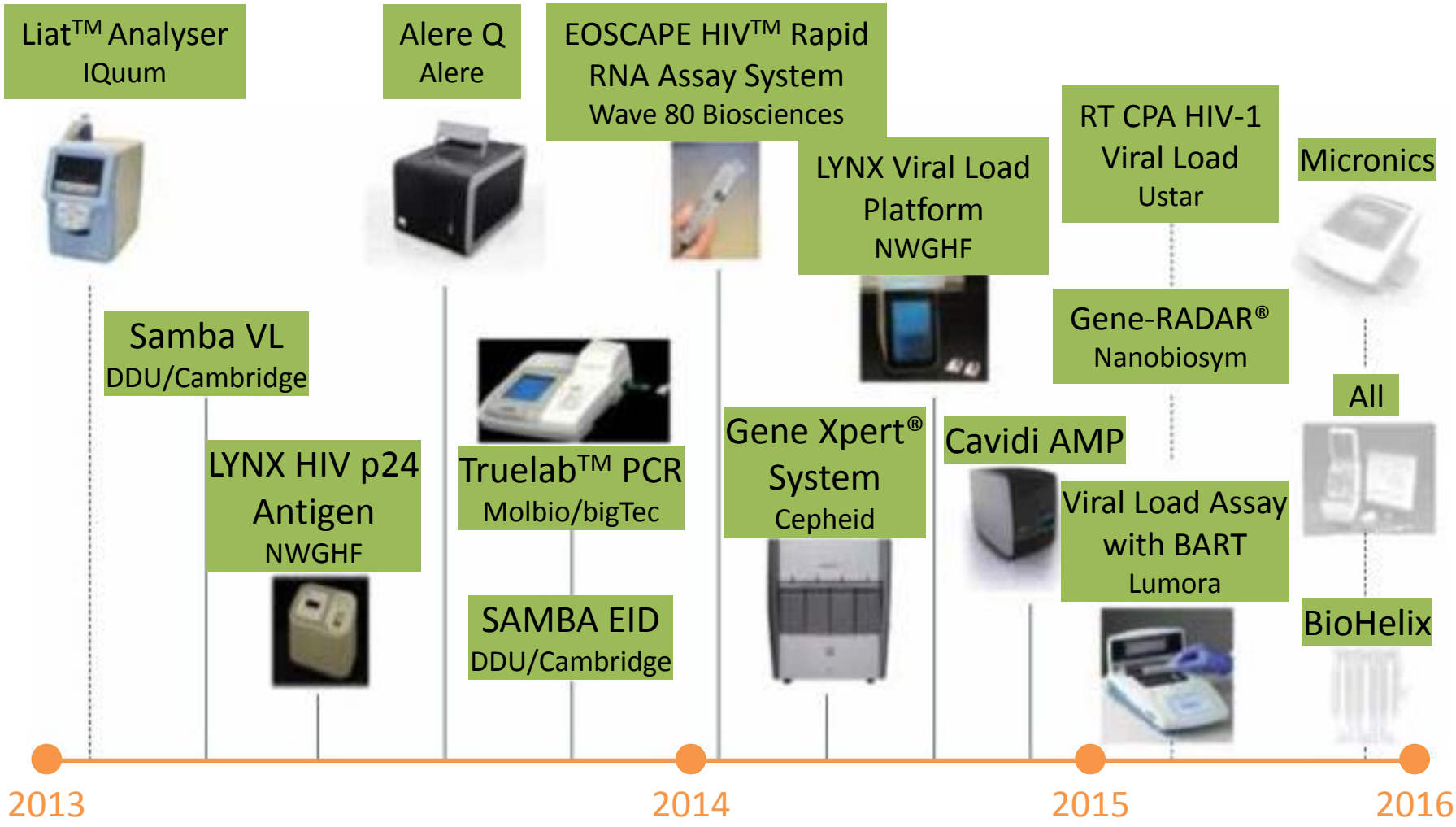
1. Dunn DT, et al. AIDS 1995;9:F7–11; 2. Bourne DE, et al. AIDS 2009;23:101–6

Early Infant Diagnosis

	WHO 2013[1]	SA Guidelines[2]	DHHS Guidelines[3]	BHIVA[4]
Birth		X (high risk)	X (high risk)	X
2–4 weeks			X	
4–6 weeks	X	X	X	X (2 weeks post prophylaxis)
12 weeks				X (2 months post prophylaxis)
4–6 months			X	
2–4 weeks after stopping breastfeeding or cessation of ARV prophylaxis		X (POST BF ONLY)	X	
Symptomatic infant	X	X	X	X

1. WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf; 2. The South African Antiretroviral Treatment Guidelines 2013. Available at: http://www.sahivsoc.org/upload/documents/2013%20ART%20GuidelinesShort%20Combined%20FINAL%20draft%20guidelines%2014%20March%202013.pdf; 3. DHHS. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. July 31, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf; 4. BHIVA guidelines for the management of HIV infection in pregnant women 2012. Available at: http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/hiv1030_6.pdf

Point-of Care EID Tests



WHO supplement to the 2013 consolidated guidelines. Available at: http://apps.who.int/iris/bitstream/10665/104264/1/9789241506830_eng.pdf?ua=1

When To Start ART

Age	WHO 2013[1]	SA guidelines[2]	DHHS (USA)[3]	BHIVA[4]
<1 year	Start all	Start all	Start all	Start all
1–3 years	Start all	Start all	CDC B/C or VL >100 000 c/mL or CD4 <1000 cells/µl/25%	CDC B/C or CD4 <1000 cells/µl/25%*
3–5 years	Start all	Start all	CDC B/C or VL >100 000 c/mL or CD4 <750 cells/µl/25%	CDC B/C or VL >100 000 c/mL or CD4 <500 cells/µl/20%*
>5 years	WHO Stage 3/4 or CD4 <500 cells/µl (prioritize <350 cells/µl)	WHO Stage 3/4 or CD4 <350 cells/µl	CDC B/C or VL >100 000 c/mL or CD4 <350 or 500 cells/µl	CDC B/C or CD4 <350 or 500 cells/µl

*consider VL >100 000 c/mL

1. WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf; 2. The South African Antiretroviral Treatment Guidelines 2013. Available at: http://www.sahivsoc.org/upload/documents/2013%20ART%20GuidelinesShort%20Combined%20FINAL%20draft%20guidelines%2014%20March%202013.pdf; 3. DHHS. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. July 31, 2012. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/perinatalgl.pdf; 4. BHIVA guidelines for the management of HIV infection in pregnant women 2012. Available at: http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/hiv1030_6.pdf

ART initiated before 12 weeks reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study

Avy Violari, Mark Cotton, Di Gibb, Abdel Babiker, Jan Steyn, Patrick Jean-Philippe, James McIntyre

PHRU, University of Witwatersrand; KID-CRU, Stellenbosch University; MRC-CTU UK; DAIDS NIAID, NIH

Violari A, et al. IAS 2007 abstract WESS103

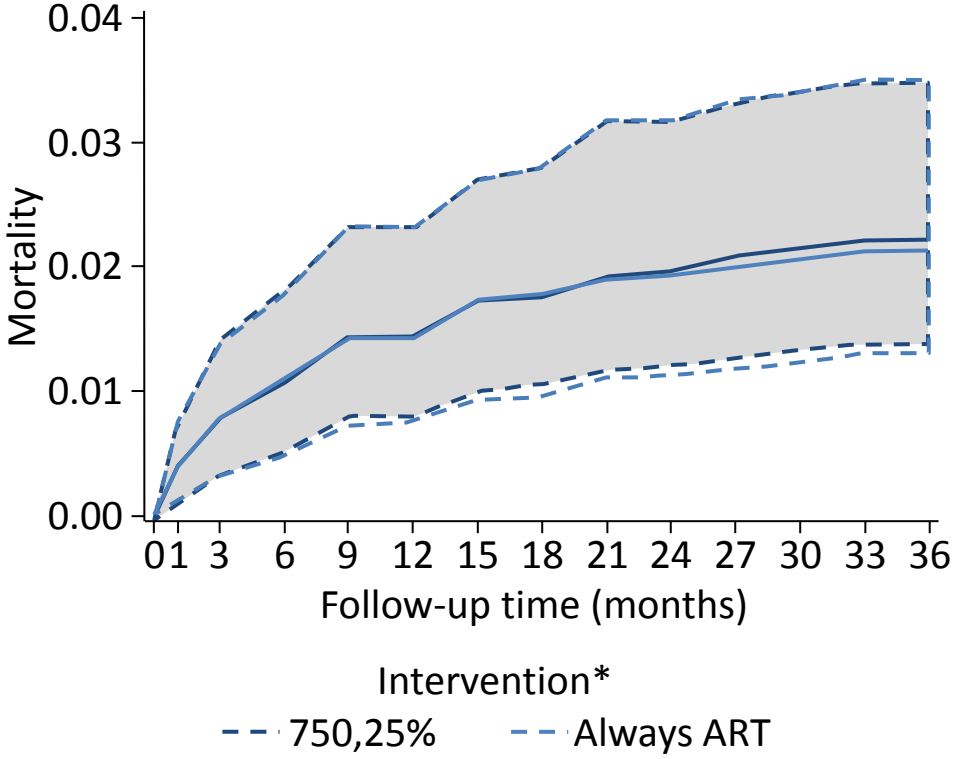
Mortality Rates

Variable	Early Treatment (arm 2/3) n=252	Deferred Treatment (arm 1) n=125	Total n=377
Died (%)	10 (4%)	20 (16%)	30 (8%)
Person Years of follow-up	167	79	246
Rate per 100 PY (95% CI)	6.0 (2.9; 10)	25.3 (15.5; 39.0)	12.2 (8.2; 17.4)
Hazard Ratio			0.24 (0.11; 0.51)
P-value			0.0002

Violari A, et al. IAS 2007 abstract WESS103

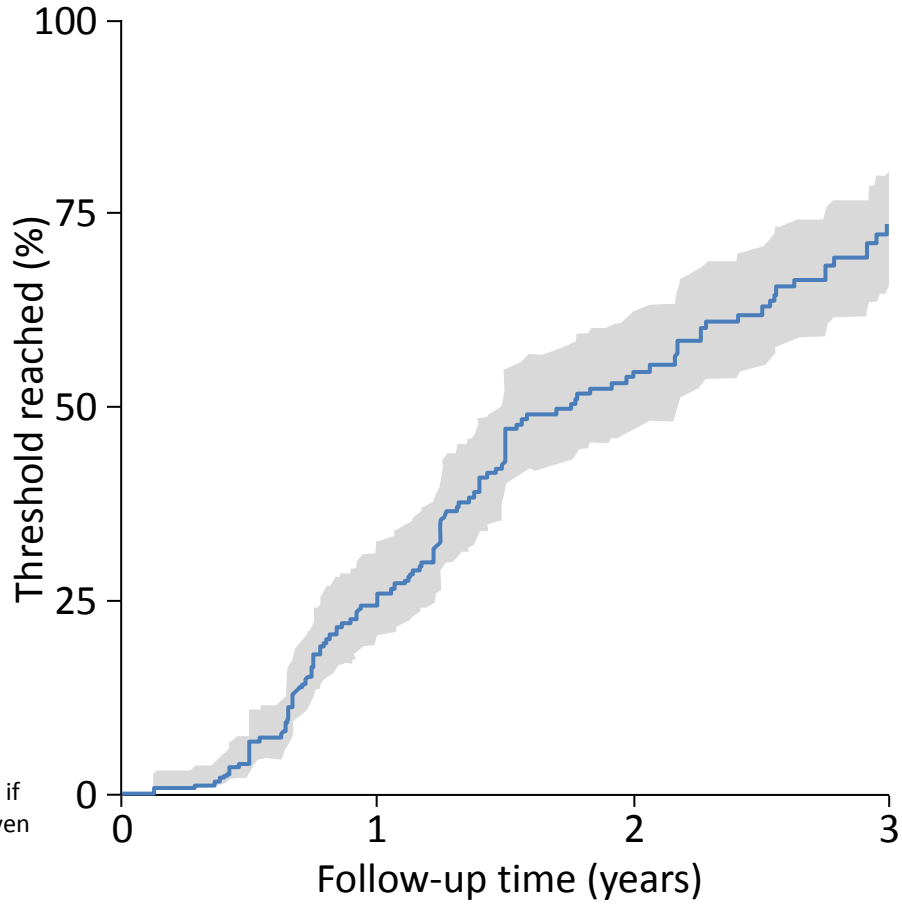
When To Start ART in Children Aged 2–5 Years: A Collaborative Causal Modelling Analysis of Cohort Studies from Southern Africa

Estimated cumulative mortality for immediate vs. deferred ART



*Estimated cumulative mortality (including 95% bootstrap CI, dashed lines) over 3 y if ART was given irrespective of CD4 count and CD4% ('always ART') and if ART was given if the CD4 count was below 750 cells/mm3 or the CD4% was below 25% ('750,25%')

Estimated probability of falling below a CD4 count of 750 cells/mm^3 or a CD4 of 25%



Schomaker M, et al. Plos Medicine 2013;10:e1001555

What To Start

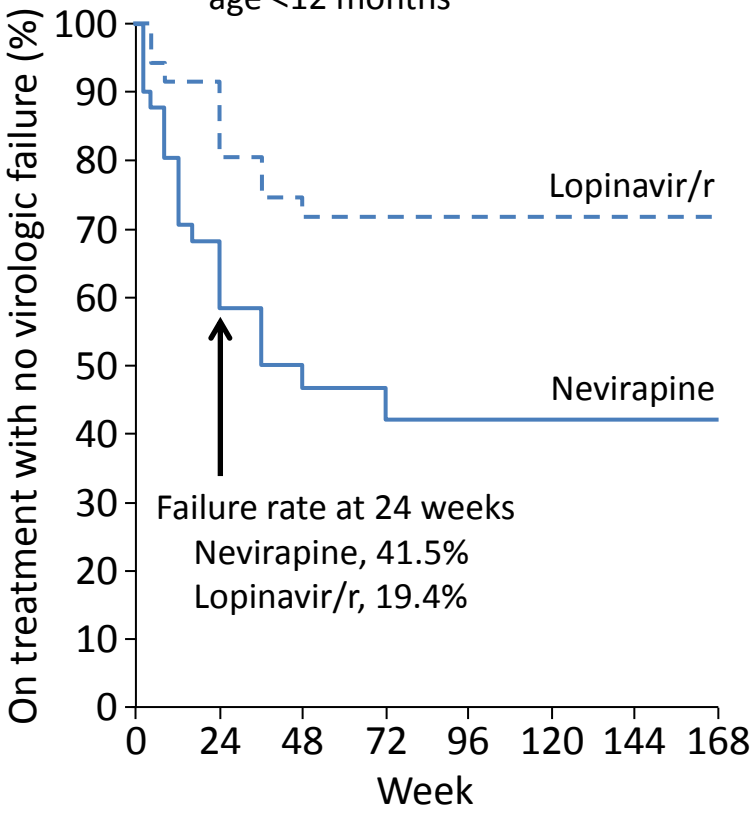
Summary of first-line ART regimens for children younger than three years

Preferred regimens	ABC or AZT + 3TC + LPV/r
Alternative regimens	ABC or AZT + 3TC + NVP
Special circumstances	d4T + 3TC + LPV/r d4T + 3TC + NVP

WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

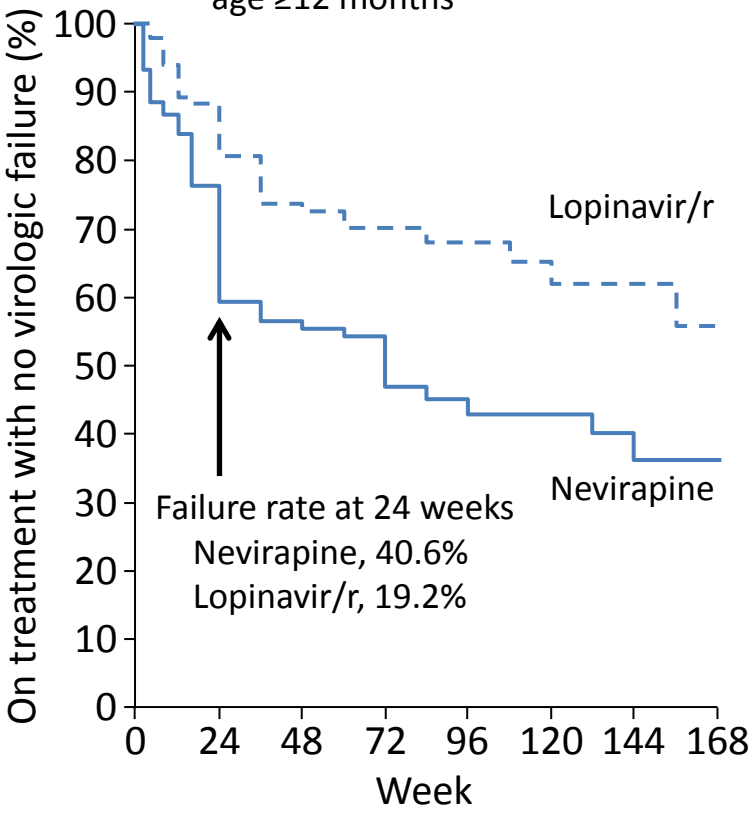
Nevirapine vs. Ritonavir-boosted Lopinavir for HIV-infected Children

Time to virologic failure or treatment discontinuation, age <12 months



No. at risk								
Nevirapine	41	28	15	10	5	3	2	2
Lopinavir/r	36	33	25	13	7	6	5	3

Time to virologic failure or treatment discontinuation, age ≥12 months



No. at risk								
Nevirapine	106	81	53	37	20	17	10	5
Lopinavir/r	104	92	68	41	26	20	12	6

Violari A, et al. N Engl J Med 2012;366:2380–9

WHO 2013: Summary of Recommended ART Regimens for Children who need TB

Recommended regimens for children and adolescents initiating ART while on TB treatment		
Younger than 3 years		Two NRTIs + NVP, ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)
3 years and older		Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)
Recommended regimen for children and infants initiating TB treatment while receiving ART		
Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)	**Younger than 3 years**	Continue NVP, ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)
	3 years and older	If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC)

WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

WHO 2013: Summary of Recommended ART Regimens for Children who need TB Treatment

Recommended regimen for children and infants initiating TB treatment while receiving ART		
Child on standard PI-based regimen (two NRTIs + LPV/r)	**Younger than 3 years**	Triple NRTI (AZT + 3TC + ABC) or Substitute NVP for LPV/r, ensuring that dose is 200 mg/m^2 or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose
	3 years and older	**If the child has no history of failure of an NNRTI-based regimen:** Substitute with EFV or Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose **If the child has a history of failure of an NNRTI-based regimen:** Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r consider adding RTV to achieve the full therapeutic dose Consider consultation with experts for constructing a second-line regimen

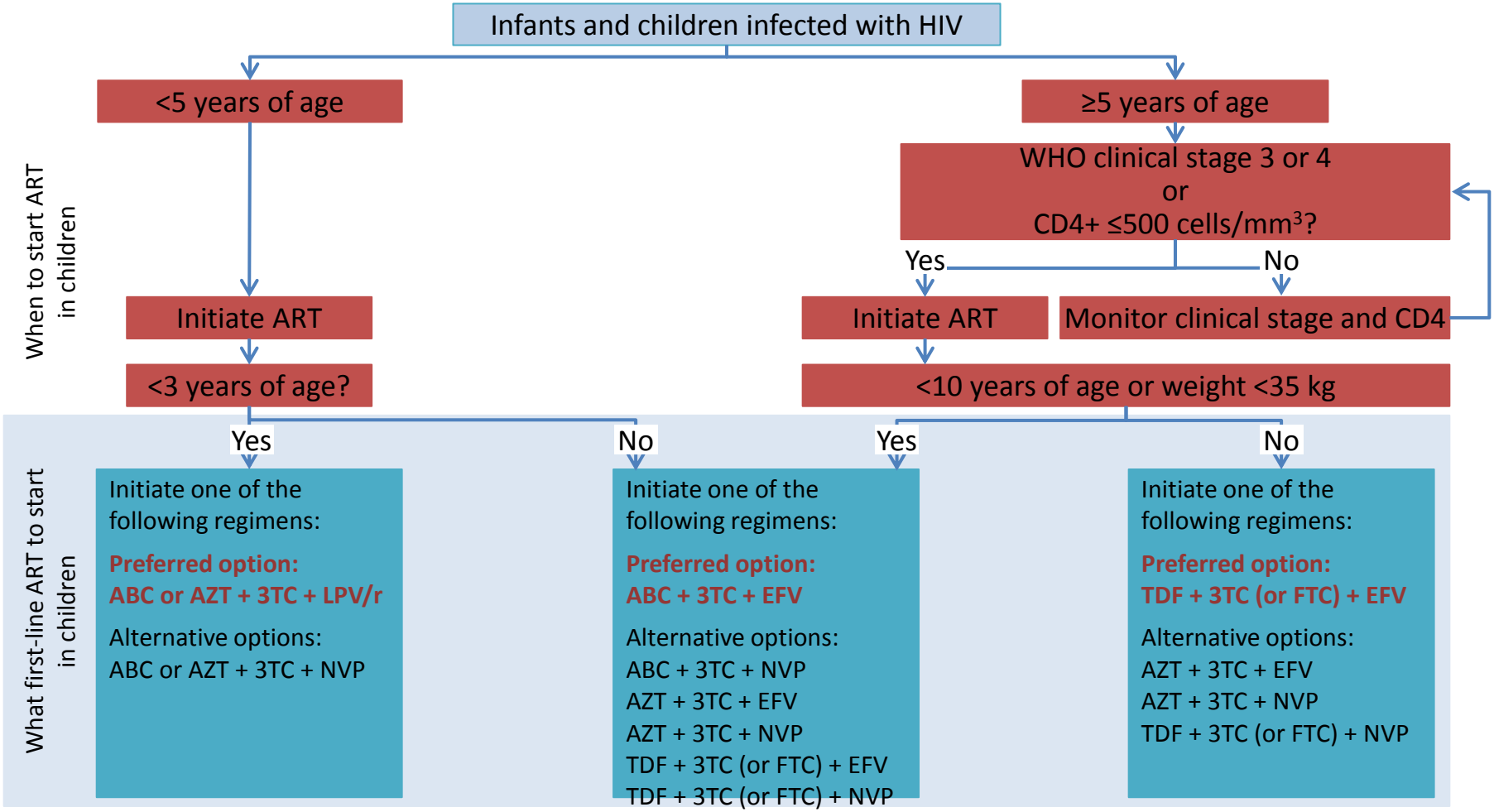
WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

WHO 2013: Summary of Recommended First-line ART Regimens for Children and Adolescents

	Children 3 years to less than 10 years and adolescents <35 kg	Adolescents (10 to 19 years) ≥35 kg
Preferred	ABC + 3TC + EFV	TDF + 3TC (or FTC) + EFV
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Special circumstances	d4T + 3TC + EFV d4T + 3TC + NVP	ABC + 3TC + EFV ABC + 3TC + NVP

WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

Algorithm for the WHO 2013 Recommendations for Children



WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

When To Switch?

All populations

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure
  (strong recommendation, low-quality evidence)
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure
  (strong recommendation, moderate-quality evidence)

WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

Treatment Failure Pathway

- Detectable Viral Load:

  ≠ Change of regimen

  = Call to action – Intensified adherence

Pediatric Enhanced Adherence Counseling Worksheet

DATE (MONTH 1):_____

STEP 1: REVIEW EDUCATION
Who attended literacy classes? _____
Who gives medication? _____

STEP 2: REVIEW MEDICATION
What is the name of medication?
_____
Where medications are kept? _____
Agreed upon time? _____
Review doses? _____
Number of late/ missed doses within the last 7 days
_____
Reason for missing doses _____
Can you tell me about the changes noted in the child's health? _____
Is the child taking any other medication or use any herbal medication? _____

STEP 3: PATIENT'S REASON FOR HIGH VL
What is causing the VL to be high according to caregiver? _____
What is Viral Load? _____
What is High Viral Load? _____
What is Suppressed Viral Load? _____

STEP 4: STORING MEDS/EXTRA DOSES
Emergency supply will be carried in: _____

STEP 5: PATIENT'S SUPPORT SYSTEM
What reminders do you have? _____
Who supports with giving treatment? _____

STEP 6: DISCUSS ADHERENCE ISSUES
Adherence difficulties: _____
Mistakes: _____
How do you plan to solve this problem? _____
_____

STEP7: PLANNING FOR TRIPS
Regular travel location: _____
Remind the pt. to plan for enough treatment.

STEP 8: GETTING TO APPOINTMENTS
How do you get to clinic? _____
Back-up plan to get to clinic_____

STEP 9: HOMEWORK & WAY FORWARD
Any questions/Homework/Plan of Action_____
_____
_____
Your VL will be repeated in
_____

Next visit date: _____

DATE (MONTH 2):_____

STEP 1: REVIEW DIARY/PLAN OF ACTION
Check Diary: _____
_____
_____
_____
_____
Plan of Action: _____
_____
_____
_____

STEP 2: PILL COUNT/MISTAKES IN ADHERENCE
Comment on Pill Count: _____
_____
Thoughts to deal with mistakes *AND* learn from mistakes
_____
_____

STEP 3: FOLLOW-UP REFERRAL SERVICES
Did you attend? _____
If yes, what was your experience?
_____
_____

STEP 5: REVIEW & PLAN A WAY FORWARD
Remind patient when VL will be repeated
Next visit date: _____

DATE (MONTH3):_____

STEP 1: DISCUSS ADHERENCE DIFFICULTIES/ PROBLEMS
Adherence difficulties_____
_____
_____
_____
_____
Problem solve_____
_____
_____

STEP 2: FOLLOW-UP ON REFERRAL SERVICES IF APPROPRIATE
How is it going? _____
_____

STEP 3: TAKE VIRAL LOAD
and any other blood tests needed

STEP 4: PLAN A WAY FORWARD
Discuss way forward if:
- VL result is low
- VL result is high

Next visit date: _____

DATE (MONTH 4):_____

STEP 1: DISCUSS VIRAL LOAD RESULTS

SUPPRESSED: VL < 400
Congratulate and encourage patient!

NOT SUPPRESSED: VL > 400
Refer to VL flowchart to assess regimen change.
If appropriate discuss new regimen, dosing schedule and possible side-effects.
Take baseline bloods, discuss with doctor

Review previous sessions

DISCUSS DIFFICULTIES/ PROBLEMS
Problem_____
_____
_____
Plan:
_____
_____

New dosing time:
_____
_____

STEP 2: PLAN A WAY FORWARD
Next visit date:
_____

Patient name: _____
Date of Birth: _____
Folder no: _____
Clinic: _____

WHO Definitions of Clinical, Immunological and Virological Failure for the Decision to Switch ART Regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodefiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure
Immunological failure	**Adults and adolescents** CD4 count falls to the baseline (or below) or Persistent CD4 levels below 100 cells/mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count A systematic review found that current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. The predicted value would be expected to be even lower with earlier ART initiation and treatment failure at higher CD4 cell counts. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
	Children Younger than 5 years: Persistent CD4 levels below 200 cells/mm^3 or <10% Older than 5 years: Persistent CD4 levels below 100 cells/mm^3	
Virological failure	Plasma viral load above 1000 copies/mL based on two consecutive viral load measurements after 3 months, with adherence support	The optimal threshold for defining virological failure and the need for switching ART regimen has not been determined An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed Assessment of viral load using DBS and point-of-care technologies should use a higher threshold

WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

What To Switch To?

Summary of preferred second-line ART regimens
for adults, adolescents, pregnant women and children

Second-line ART			Preferred regimens	Alternative regimens
Adults and adolescents (≥10 years), including pregnant and breastfeeding women			AZT + 3TC + LPV/r[a] AZT + 3TC + ATV/r[a]	TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r
Children	**If a NNRTI-based first-line regimen was used**		ABC + 3TC + LPV/r[b]	ABC + 3TC + LPV/r[b] TDF + 3TC (or FTC) + LPV/r[b]
	If a PI-based first-line regimen was used	**<3 years**	No change from first-line regimen in use[c]	AZT (or ABC) + 3TC + NVP
		3 years to less than 10 years	AZT (or ABC) + 3TC + EFV	ABC (or TDF) + 3TC + NVP

[a]DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.
[b]ATV/r can be used as an alternative to LPV/r for children older than six years.
[c]Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

WHO. The use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2013 revision. Available at: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf

Maintaining Good Adherence in Children

- Challenging:
  - Young child:
    - Appropriate formulation for the age of the child
    - Fitting the ART regimen into the child's schedule
    - ART fatigue
  - Adolescent and pre-adolescent:
    - Disclosure
    - Challenging of authority / Development of an individual personality
    - Ease of taking chronic medication

New Drugs/New Recommendations of Established Drugs

- **Abacavir**
  - Once daily dosing
- **Efavirenz**
  - FDA approved in children >3/12 and >3.5 kg
- **Nevirapine**
  - XR or extended release in those >6 years
- **Darunavir**
  - Once daily dosing only in those >12 years
  - Although FDA approved in those <12 years, not enough data for once daily dosing

- **Raltegravir**
  - FDA approved for infants and children >4 weeks >3 kg
  - Sachets for reconstitution (100mg/sachet)
  - Chewable tablet 100mg and 25 mg (Section 21)
  - Neonatal dose – Impaact P1110
  - MCC (registered >16yrs)

- **Dolutegravir**
  - FDA approved > 12 yrs and > 40kg - 50 mg oral tablet – Daily
  - 50 mg granules/ – phase 1/2 Trials started

- **Stribild**
  - (elvitegravir/cobicistat/emtricitabine/tenofovir)
  - found to be safe, effective in adolescents

New Formulations for Children

- Partnership between CIPLA and DNDi
- Specially created for children <3 years of age
- By 2015
- 2 new FDCs plus new ritonavir
- Ritonavir
  - For babies with TB and HIV
  - Granules
- FDCs
  - 4-in-1 (LPV/r/AZT/3TC and LPV/r/ABC/3TC)
  - Granules
  - Sprinkled over food/mixed with milk
  - Palatable (masked taste)
  - No refrigeration