Pediatric Antiretroviral Treatment Optimization: A Changing Landscape

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Overview

- Background and Rationale for Optimization
- Update on WHO 2019 recommendations for Pediatric ART
- New Pediatric ARV formulations
- The Optimal Formulary and Limited-use List
- Transition planning
- Q&A

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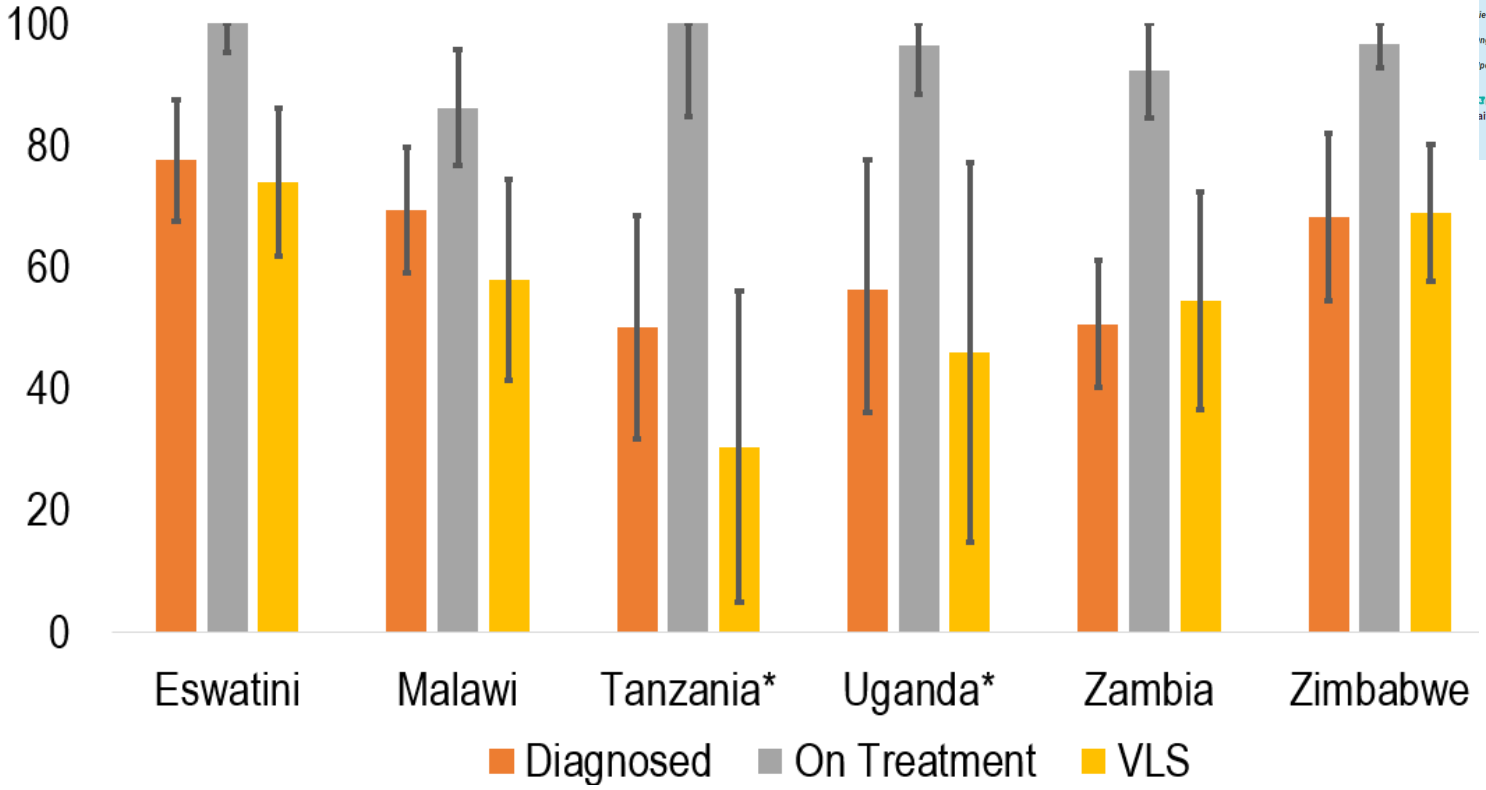
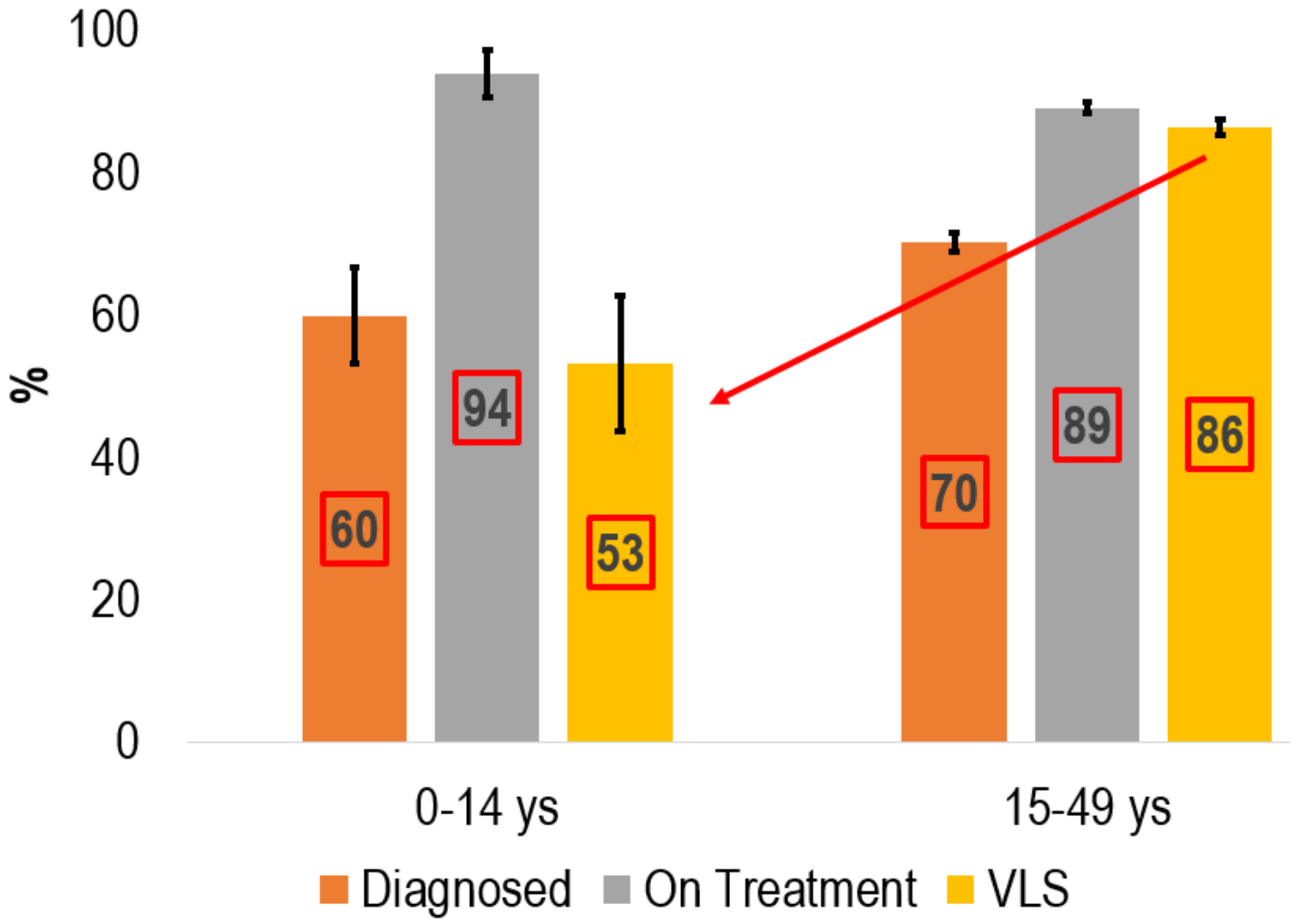
Population-based HIV Impact Assessment (PHIA): Measuring 90-90-90

Gaps in 1st and 3rd 90 for children 0-14 years



Source: Saito, 10th pediatric workshop, 2019

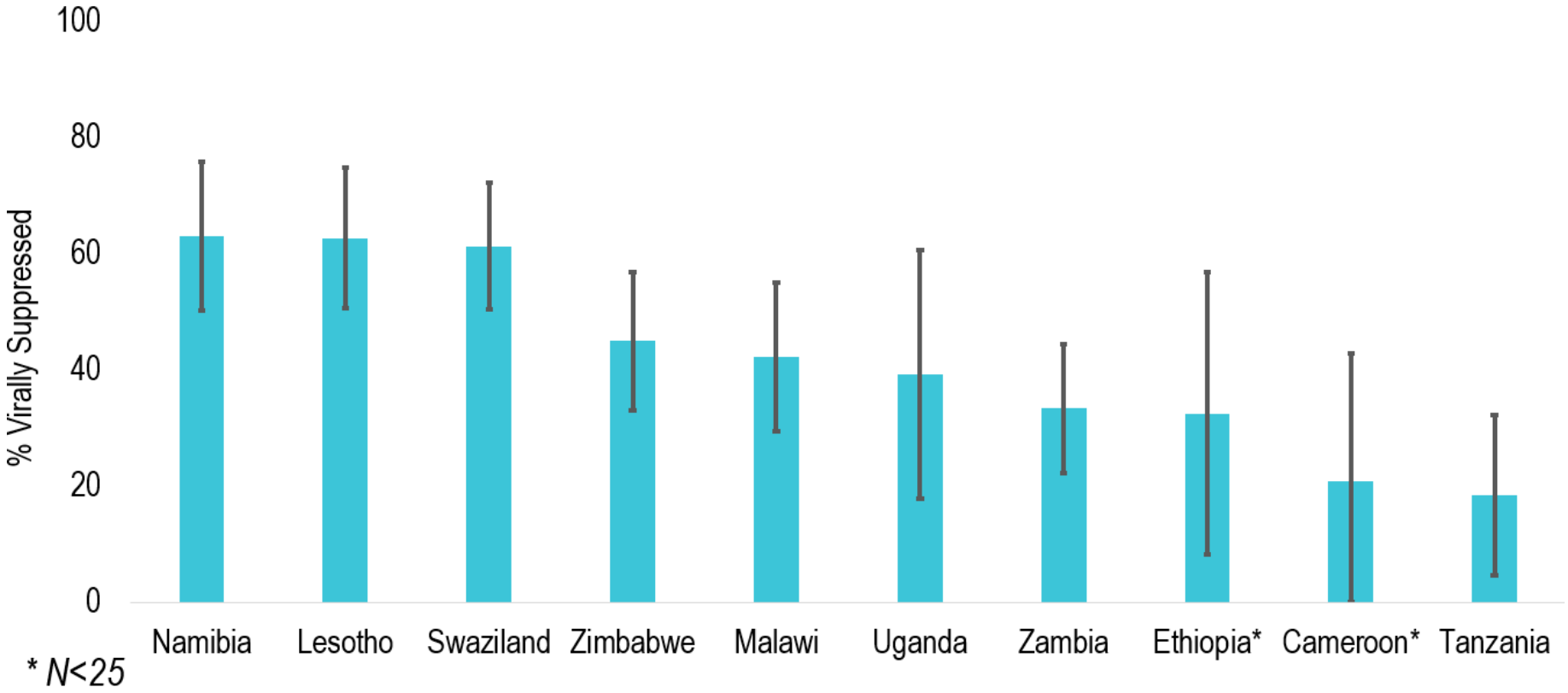
Measuring 90-90-90: Viral load suppression in children vs. adults



**Pooled estimates from 6 countries, PHIA 2016-2018*

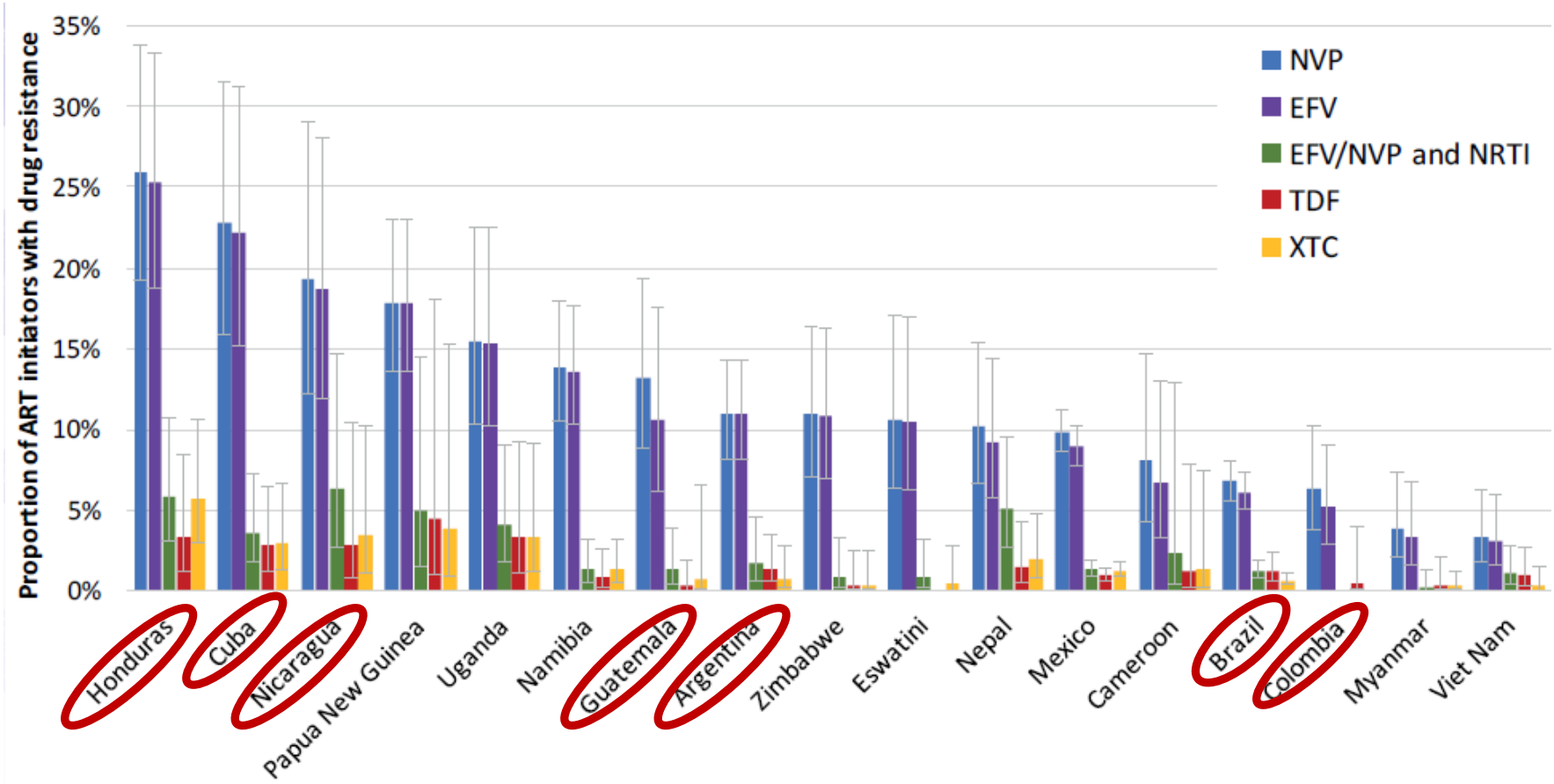
Source: Saito, 10th pediatric workshop, 2019

Viral load suppression (VLS) among *all* children living with HIV, 0-14y (n=683)



Source: Saito, 10th pediatric workshop, 2019

Pretreatment drug resistance among first-line ART initiators by country and drug



EFV: efavirenz; NVP: nevirapine; NRTI: nucleoside reverse-transcriptase inhibitors; TDF: tenofovir disoproxil fumarate; XTC: emtricitabine (FTC) or lamivudine (3TC).

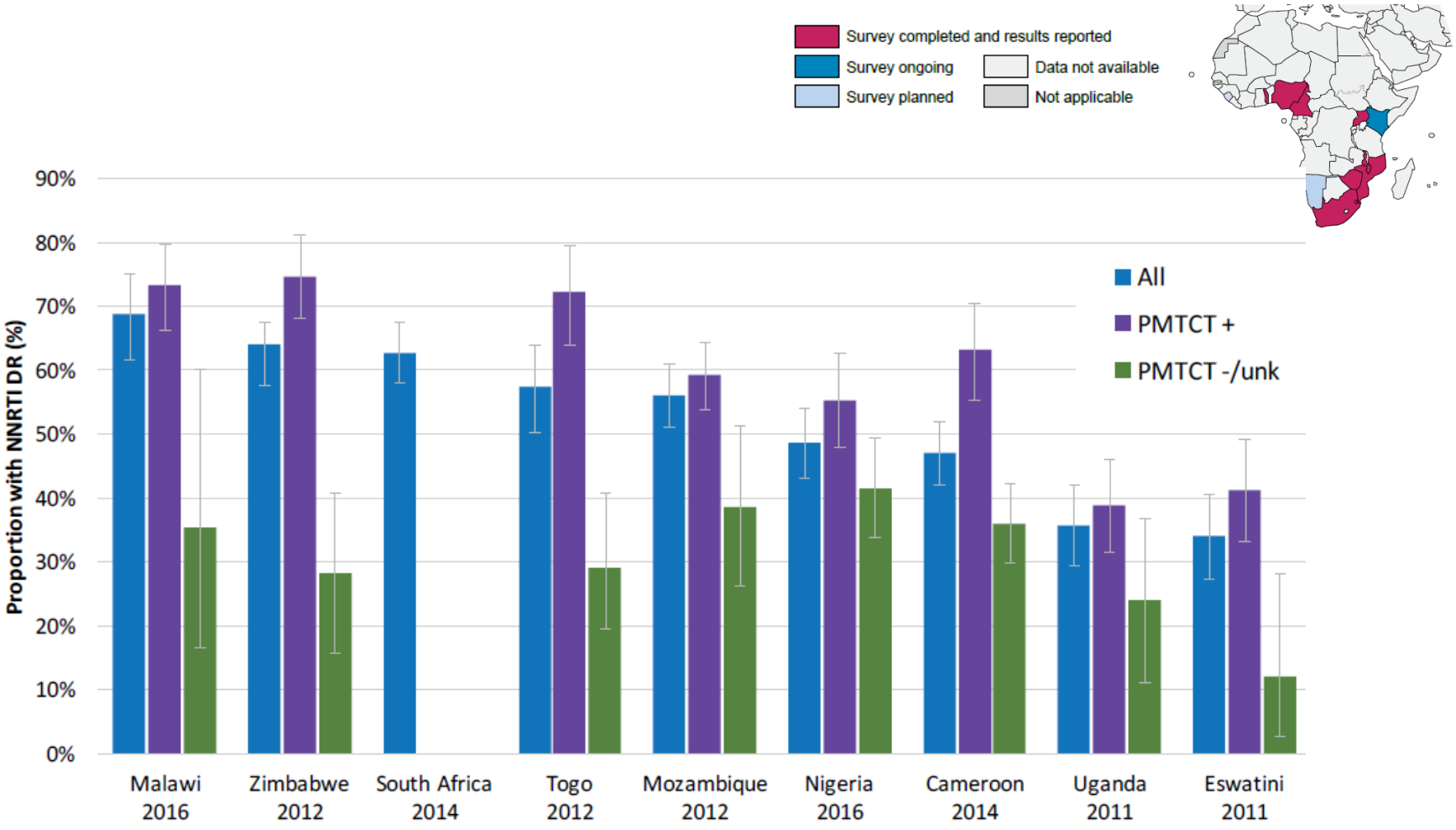
Source: WHO HIV Drug Resistance Report 2019

NNRTI pretreatment drug resistance from countries reporting national survey data to WHO 2014 – 2018: Region of the Americas

WHO region	Country	Survey year	Prevalence of NNRTI PDR				
			All (women and men)	Women	Men	ART initiators reporting being ARV drug naive	ART initiators reporting previous ARV drug exposure
Region of the Americas	Argentina	2014					
	Brazil	2014					
	Colombia	2016					
	Cuba	2017					
	Guatemala	2016					
	Honduras	2016					
	Mexico	2017					
	Nicaragua	2016					

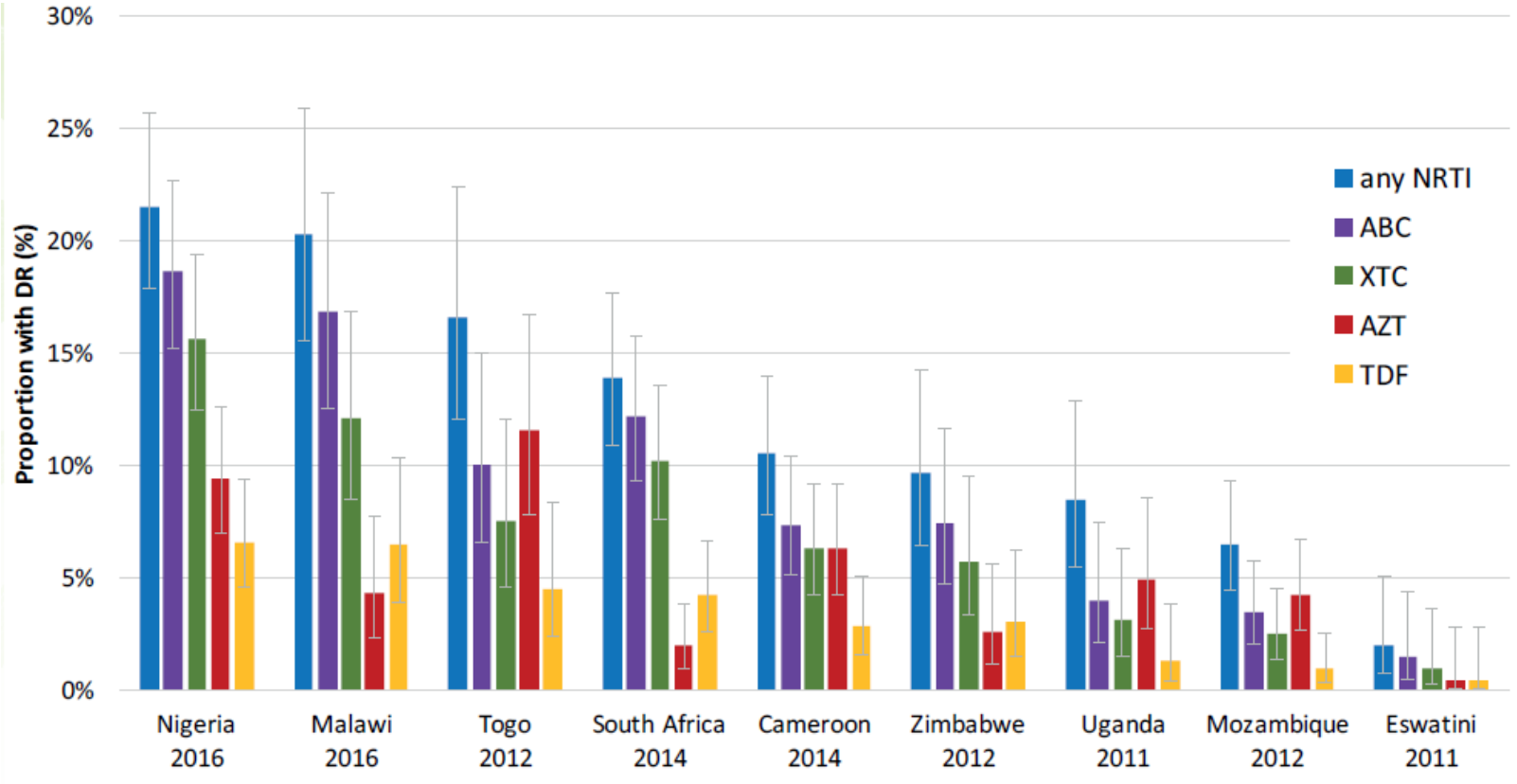
Prevalence of PDR to EFV and/or NVP: <10% 10-30% >30%

WHO national pretreatment HIV drug resistance surveys among infants newly diagnosed with HIV and treatment naïve 2012-2018: NNRTI resistance



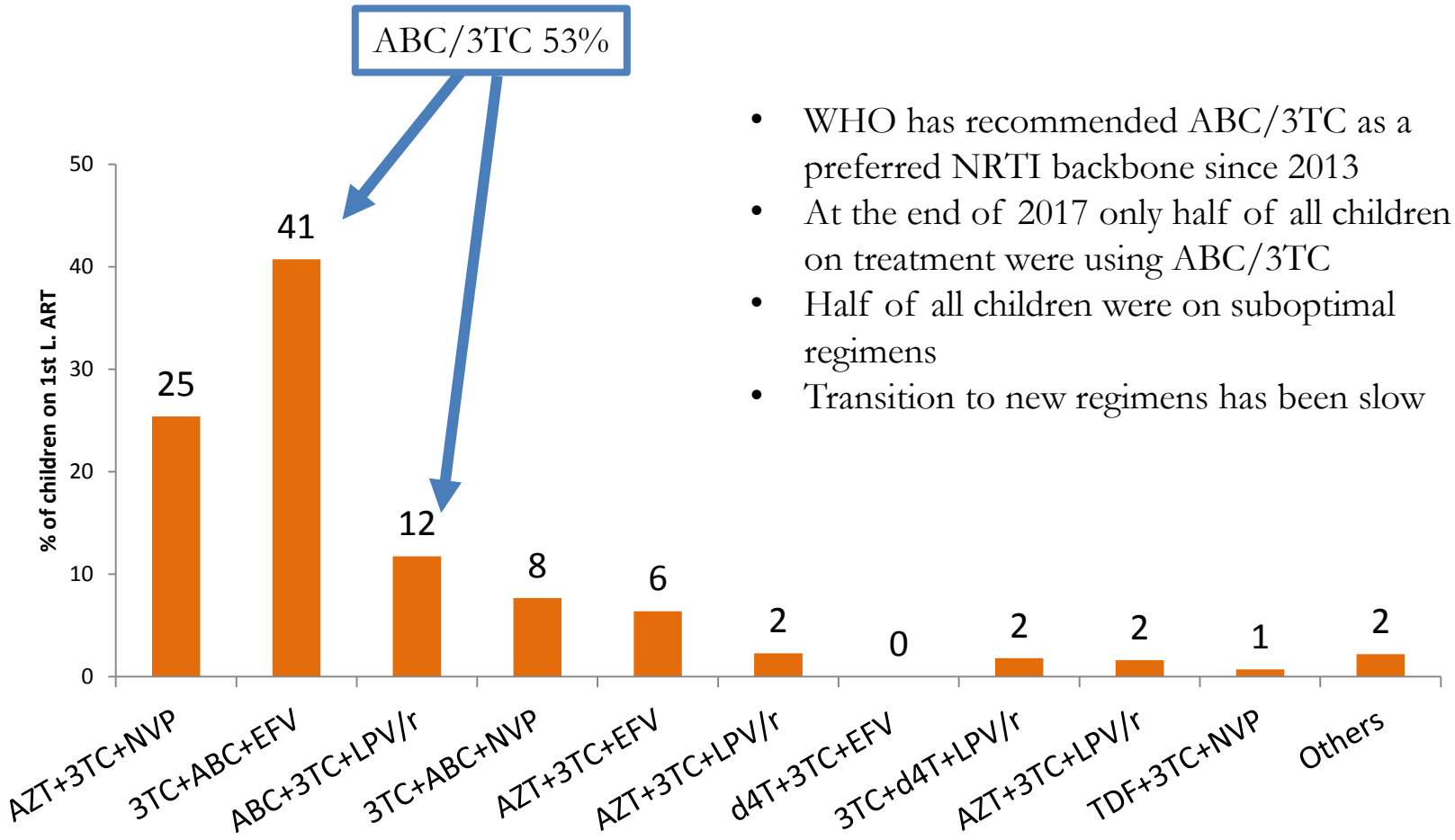
Source: WHO HIV Drug Resistance Report 2019

WHO national pretreatment HIV drug resistance surveys among infants newly diagnosed with HIV and treatment naïve 2012-2018: NRTI resistance



Legend: ABC: abacavir; AZT: zidovudine; NRTI: nucleoside reverse-transcriptase inhibitor; TDF: tenofovir disoproxil fumarate; XTC: emtricitabine (FTC) or lamivudine (3TC)

From policy to practice: 1st line Pediatric ARV regimen use at the end of 2017



- WHO has recommended ABC/3TC as a preferred NRTI backbone since 2013
- At the end of 2017 only half of all children on treatment were using ABC/3TC
- Half of all children were on suboptimal regimens
- Transition to new regimens has been slow

World Health Organization

Source: 2018 WHO Global ART use survey

Better treatment options are needed

OPTIMAL ARVs
Efficacious
Low toxicity
Well tolerated and easy to take
Durable/High genetic barrier to resistance
Better sequencing/switching
Harmonized across populations (Preg, TB, Peds)
Reduces cost*

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WHO 2019 Pediatric ART Recommendations

Move away from NNRTI-based regimens

Introduce DTG as soon as possible

Use the most potent non-NNRTI option

	Neonates	Children
Preferred	AZT + 3TC +RAL[1]	ABC + 3TC + DTG[2]
Alternatives	AZT + 3TC + NVP	ABC + 3TC + LPV/r ABC + 3TC + RAL[3] TAF[4] + 3TC (or FTC) +DTG
Special circumstances[5]	AZT + 3TC + LPV/r	ABC + 3TC +NVP ABC + 3TC + EFV AZT + 3TC + EFV AZT + 3TC + RAL AZT + 3TC + LPV//r AZT + 3TC + NVP

[1]Neonates starting ART with a RAL-based regimen should transition to an LPV/r solid formulation as soon as possible

[2]For age and weight groups with approved DTG dosing (50 mg adult tablet from 20 kg, TLD can be used in adolescents weighing more than 30 kg)

[3]RAL should only be used as an alternative regimen only if LPV/r solid formulations are not available

[4] For age and weight groups with approved TAF dosing (adult dose of TAF can be used in children weighing 25kg or more)

[5] In cases where no other alternatives are available

World Health Organization

2019 WHO Guidelines Update- Sequencing Options

Sequencing Options for Pediatric Populations		
First line	Second line*	Third line
2 NRTIs + LPV/r	2 NRTIs + DTG**	DRV/r + DTG**** +/- 1-2 NRTIs. Where possible consider using optimization using genotyping
2 NRTIs + EFV or NVP	2 NRTIs + DTG***	
2 NRTIs + DTG or RAL	2 NRTIs + ATV/r or LPV/r	

* Optimized NRTI backbone should be used

** Applies to children for who DTG doing is available, RAL is preferred second line if DTG is not available

*** Applies to children for who DTG doing is available, ATV/r or LPV/r is preferred second line if DTG is not available

**** DTG-based third line following use of INSTI must be administered twice-daily

World Health Organization

2019 WHO Guidelines Update

What's New

- DTG-containing regimens for all infants and children 4 weeks and older when dosing and formulations are available
- RAL granules for neonatal treatment
- LPV/r or RAL as alternative first-line for infants and children
- NNRTI-containing regimens only for special circumstances when no alternative is available
- DTG or RAL containing second-line after failure on LPV/r or NNRTI-containing first-line
- bPI-based regimen after failure in INSTI-containing first-line
- TAF-containing regimens an alternative for infants and children 4 weeks and older when dosing and formulations are available

Anticipated Trends

- Increasing use of ABC/3TC as preferred NRTI backbone
- Decreasing use of NNRTI-containing regimens
- Increasing use of INSTI-containing first and second-line regimens
- Increasing demand for RTV formulations to super-boost during TB treatment

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New option for neonates: RAL granules

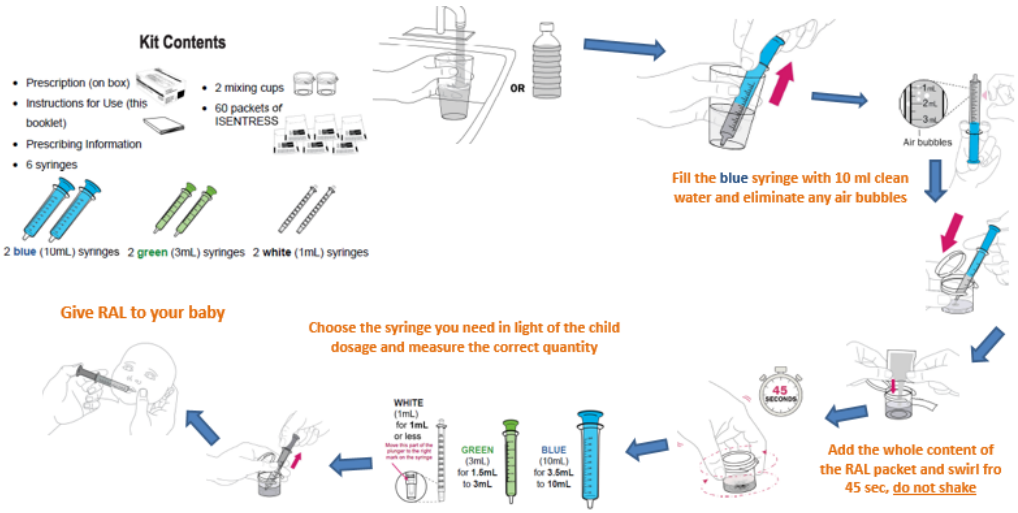
- November 22, 2017: FDA approved expanded indication of raltegravir to include full term* neonates from birth- 4 weeks, weighing at least 2 kg
- Consider in programs introducing birth testing
- Not yet approved for pre-term or infants <2kg
- RAL granules in 100mg packets- each packet to be mixed with 5mL of water to make suspension of 20mg/mL

Age	Dose
Birth-7 days	1.5 mg/kg once-daily
8-28 days	3mg/kg twice-daily
≥ 4 weeks	6 mg/kg twice-daily

*≥ 37 weeks gestational age

Feasibility administering RAL granules

Step 1: Get ready
Step 2: Fill a clean glass with water
Step 3: Fill the blue syringe with water
Step 4: Check for air bubbles
Step 5: Add the 10mL of water to the mixing cup
Step 6: Add ISENTRESS to the mixing cup
Step 7: Mix ISENTRESS and water
Step 8: Check your prescription
Step 9: Choose the syringe you need
Step 10: Measure ISENTRESS
Step 11: Check for air bubbles
Step 12: Give ISENTRESS to your child
Step 13: Clean up



Body Weight (kg)	Volume (Dose) of Suspension to be Administered
Birth to 1 Week - Once daily dosing*	
2 to less than 3	0.4 mL (4 mg) once daily
3 to less than 4	0.5 mL (5 mg) once daily
4 to less than 5	0.7 mL (7 mg) once daily
1 to 4 Weeks - Twice daily dosing †	
2 to less than 3	0.8 mL (8 mg) twice daily
3 to less than 4	1 mL (10 mg) twice daily
4 to less than 5	1.5 mL (15 mg) twice daily

*The dosing recommendations are based on approximately 1.5 mg/kg/dose.
†The dosing recommendations are based on approximately 3 mg/kg/dose.

Raltegravir (RAL) chewable tablets

- 25mg and 100mg scored chewable tablets FDA approved for children ≥ 2 years and ≥ 10 kg
- Chewable tablets may be "dispersed" in liquid (e.g. breastmilk)
- WHO endorses use of chewable tablets for infants and young children from 4 weeks and 3 kg
- Chewable tablets not bioequivalent to granules or film-coated adult tablet (400 mg)

MERCK

100 mg scored

25 mg

RAL	3.0-5.9 kg		6.0-9.9 kg		10.0-13.9 kg		14.0-19.9 kg		20.0-24.9 kg		25.0-34.9 kg	≥ 35 kg
	am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
25mg	1	1	2	2	3	3	4	4	6	6	400mg	400mg
100mg	-	-	-	-	-	-	1	1	1.5	1.5		

Harmonizing Pediatric ART Regimens: DTG

- FDA approved in children ≥30kg
- EMA approved in children ≥ 6 yrs/ ≥ 15kg
- WHO endorses 50mg dose in children ≥20kg
- TLD (adult) recommended in children ≥ 30kg
- **Currently available in 50mg, 25mg and 10mg tablets**
- Ongoing work to establish dosing in younger children and infants down to 4 weeks
- **Viiv developing a 5mg dispersible tablet**
- **Generic 10mg scored dispersible tablets and ABC/3TC/DTG also in development**

25 mg

10 mg

ViiV Healthcare

Pediatric DTG Dosing (FDA)	
Body weight (kg)	Dose
30- <40kg	35mg OD
NEW!	
Body weight (kg)	**Dose**
≥ 20kg	**50mg OD**

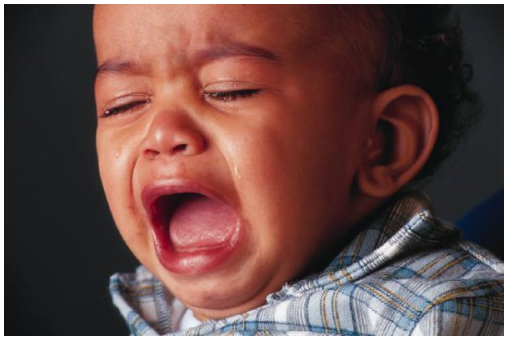
Paediatric DTG Dosing (EMA)	
Body weight (kg)	Dose
15 to less than 20	20mg OD
20 to less than 30	25mg OD
30 to less than 40	35mg OD
40 or greater	50mg OD

Paediatric DTG Dosing (WHO)

3.0-5.9 kg	6.0-9.9 kg	10.0-13.9 kg	14.0-19.9 kg	20.0-24.9 kg	25.0-34.9 kg	≥ 35 kg
-	-	-	-	50mg	24-29.9- 50mg *and* 30-34.9- TLD (300/300/DTG)	TLD (300/300/50mg)

Challenges in scaling up LPV/r based regimens for infants and children

	Children ≤ 20kg
Preferred	ABC + 3TC + DTG[2]
Alternatives	ABC + 3TC + LPV/r ~~ABC + 3TC + RAL[3]~~ TAF[4] + 3TC (or FTC) +DTG



Kaletra syrup

- Requires cold chain
- Bitter taste
- Toxic excipients
- Heavy to carry
- Hard to store

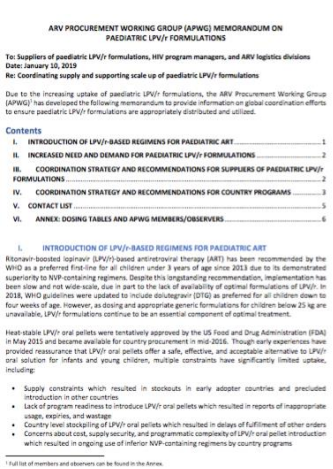
LPV/r 40 mg/10 mg oral pellets and granules

- LPV/r-based regimens were previously the preferred 1st line for infants and children <3 years, at the end of 2017 the majority of young children were still on NVP-containing regimens
- LPV/r oral pellets and granules offer a heat-stable alternative to LPV/r liquid
- LPV/r oral pellets approved by USFDA in 2015 and LPV/r granules in August 2018
- Previously manufacturing constraints limited scale-up but supply availability has improved significantly
  - Increase in supplier capacity for LPV/r pellets and granules

Supply of LPV/r pellets/granules now less of a constraint for country programs

More support for use of new LPV/r pediatric formulations is now available

APWG for procurement support



ARV PROCUREMENT WORKING GROUP (APWG) MEMORANDUM ON PAEDIATRIC LPV/r FORMULATIONS

To: Suppliers of paediatric LPV/r formulations, HIV program managers, and ARV logistics divisions
Date: January 10, 2019
Re: Coordinating supply and supporting scale up of paediatric LPV/r formulations

Due to the increasing uptake of paediatric LPV/r formulations, the ARV Procurement Working Group (APWG)[1] has developed the following memorandum to provide information on global coordination efforts to ensure paediatric LPV/r formulations are appropriately distributed and utilized.

Contents

I. INTRODUCTION OF LPV/r-BASED REGIMENS FOR PAEDIATRIC ART

Ritonavir-boosted lopinavir (LPV/r)-based antiretroviral therapy (ART) has been recommended by the WHO as a preferred first-line for all children under 3 years of age since 2013 due to its demonstrated superiority to NVP-containing regimens. Despite this longstanding recommendation, implementation has been slow and not wide-scale, due in part to the lack of availability of optimal formulations of LPV/r. In 2018, WHO guidelines were updated to include dolutegravir (DTG) as preferred for all children down to four weeks of age. However, as dosing and appropriate generic formulations for children below 25 kg are unavailable, LPV/r formulations continue to be an essential component of optimal treatment.

Heat-stable LPV/r oral pellets were tentatively approved by the US Food and Drug Administration (FDA) in May 2015 and became available for country procurement in mid-2016. Though early experiences have provided reassurance that LPV/r oral pellets offer a safe, effective, and acceptable alternative to LPV/r oral solution for infants and young children, multiple constraints have significantly limited uptake, including:

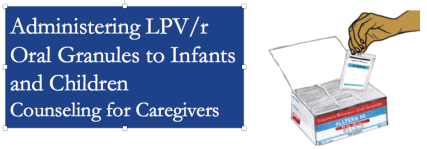
- Supply constraints which resulted in stockouts in early adopter countries and precluded introduction in other countries
- Lack of program readiness to introduce LPV/r oral pellets which resulted in reports of inappropriate usage, expiries, and wastage
- Country level stockpiling of LPV/r oral pellets which resulted in delays of fulfillment of other orders
- Concerns about cost, supply security, and programmatic complexity of LPV/r oral pellet introduction which resulted in ongoing use of inferior NVP-containing regimens by country programs

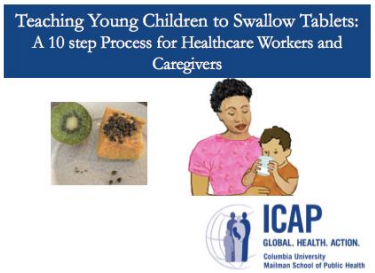
[1] Full list of members and observers can be found in the Annex.

The ARV Procurement Working Group (APWG) provides support to programs for rational procurement of LPV/r formulations and coordination of available supply

New counseling materials to support administration of LPV/r formulations

- LPV/r Pellet administration counseling cards and troubleshooting tips
- LPV/r Granule administration counseling cards (being field tested)
- Steps for teaching young children how to swallow tablets

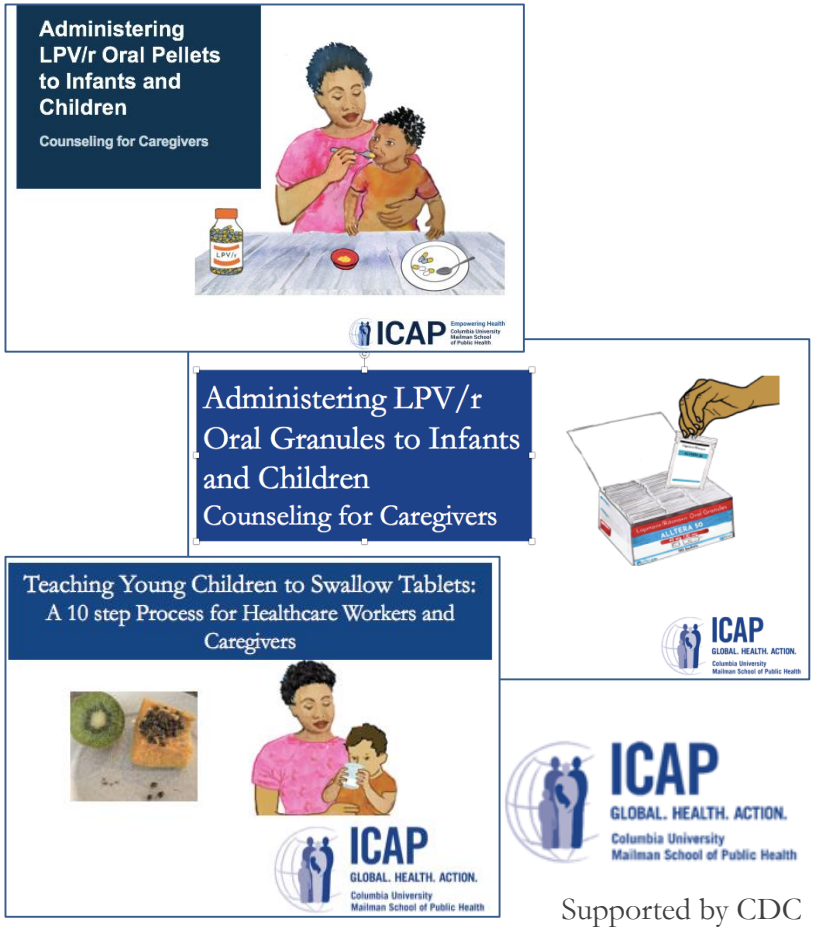




Granule counseling cards

More support for use of new LPV/r pediatric formulations is now available

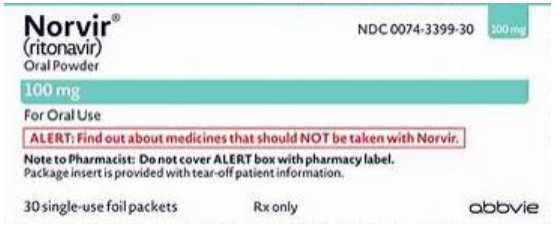
- **LPV/r Pellet Administration Counseling Cards**
  - Includes troubleshooting tips from real world experience
- **LPV/r Granule Administration Counseling Cards**
  - In field testing
- **Steps for Teaching Young Children how to Swallow Tablets in 10 Steps**
  - Uses different head positioning techniques
  - Starting with small particles and increasing in size- appropriate for use in resource-limited settings



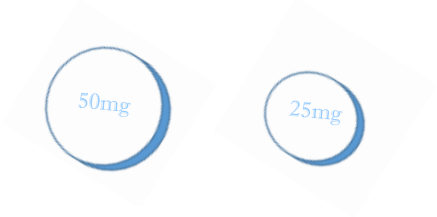
Supported by CDC

Options for RTV (boosting and superboosting)

- Ritonavir oral solution (80 mg/ml)
  - Difficult to procure
  - Short shelf life



- Ritonavir oral powder (100 mg/packet) *NEW!*
  - Available from originator
  - Cannot reliably adjust dose



- Ritonavir hs tablets (25 mg and 50 mg)
  - Not yet commercialized
  - 25 mg tablet prioritized

Superboosting LPV/r during TB treatment

Older children

- LPV/r 100mg/25mg hs tablets
- Option to sb with RTV 100mg or 25mg tablet

Infants and younger children

- LPV/r liquid or pellets
- Option to sb with RTV liquid or powder

Drug	Strength	Number of tab or mL/day											
		3-5.9 kg		6-9.9 kg		10-13.9 kg		14-19.9 kg		20-24.9 kg		25-34.9 kg	
		am	pm	am	pm	am	pm	am	pm	am	pm	am	pm
LPV/r	100mg/25 mg (hs tab)	-	-	-	-	2	1	2	2	2	2	3	3
RTV	100mg	-	-	-	-	1	1	1	2	1	2	2	2
	25mg	-	-	-	-	4	4	6	6	6	6	2 x 100mg	2 x 100mg
LPV/r	80/20mg/ mL (soln)	1	1	1.5	1.5	2	2	2.5	2.5	3	3	-	-
	40/20 (pellets)	2	2	3	3	4	4	5	5	6	6	-	-
RTV	80mg/mL (soln)	0.8	0.8	1.2	1.2	1.5	1.5	2	2	2.3	2.3	-	-
	100mg/pkt (powder)	-	-	1	1	1	1	1	2	1	2	-	-

ABC the preferred NRTI for pediatric 1st line ART

- WHO Consolidated Guidelines has recommended ABC as a preferred NRTI since 2013
- ABC/3TC 60mg/30mg scored dispersible tablet is widely available
- Concern for high pill burden, especially with once daily dosing in older children- a ABC/3TC 120mg/60mg scored dispersible tablet also now available and preferred

	Children < 3 years	Children 3 years to < 10 years
Preferred	**ABC + 3TC + LPV/r or AZT + 3TC + LPV/r**	**ABC + 3TC + EFV**

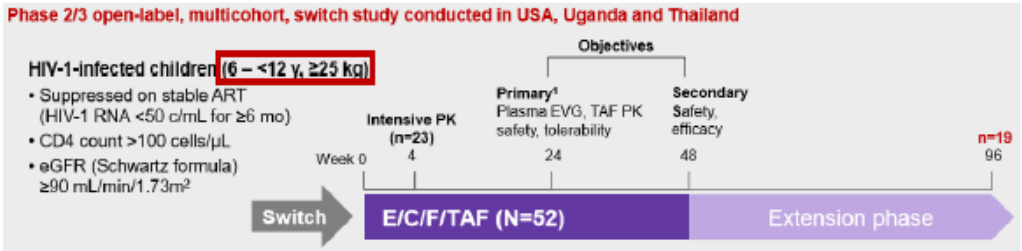
Weight Band (Kg)	Pediatric	
	ABC/3TC (60/30 mg)	ABC/3TC (120/60mg)
3-5.9	2	1
6-9.9	3	1.5
10-13.9	4	2
14-19.9	5	2.5
20-24.9	6	3
25-34.9	1 adult tab (600/300mg)	

TAF as an alternative NRTI option

Safety and Efficacy of E/C/F/TAF in Virally Suppressed Children Through 96 Weeks

Rakhamanina N et al. Pediatric HIV Workshop, July 2019, Mexico City, Abs. 22

- Switch study in virally suppressed children on ART.



- PK consistent with prior studies; viral efficacy maintained.

PK

- TAF, TFV exposures generally higher than adults but within ranges of E/C/F/TAF & B/F/TAF programs[1,2]
  - 52% higher TAF AUC_{tau}
  - 45% higher TFV AUC_{tau} 53% higher TFV C_{max}
- EVG, COBI, FTC exposures (noncompartmental analysis) within range of historical data associated with long-term safety, efficacy in E/C/F/TDF and E/C/F/TAF-treated adults and pediatrics

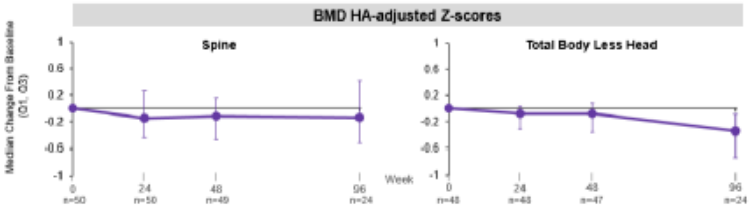
Efficacy

Virologic outcome	98% (n=51/52) had HIV-1 RNA <50 copies/mL (Week 48)
CD4 cell count and % (median)	926 CD4 cells/µL at baseline −25 cells/µL change in CD4 cell count (Week 48) −0.2% change in CD4% (Week 48)

- No Gr ≥3 AE or SAE or AE leading to drug dc. No renal AE and bone z-score consistent with age reference population.

n (%)	E/C/F/TAF (N=52)
Drug-related AE (all Grade 1)*	14 (27)
Vomiting	8 (15)
Abdominal pain	4 (7)
Headache	2 (4)
Asthenia	1 (2)
Constipation	1 (2)
Vitamin D deficiency	1 (2)
Dizziness	1 (2)
Tablet shape issue	1 (2)
Tablet size issue	1 (2)

*Participants may have had >1 AE.



Slide courtesy of Lynne Mofenson

TAF approval by U.S. FDA

	Approved in 12 - <18yrs if ≥35kg	**Approved in 6 – 12 yrs if ≥25kg**
FTC/TAF (200/25)	✓*	✓(unboosted only)
EVG/Cobi/FTC/TAF (150/150/200/10)	✓*	✓*
BIC/FTC/TAF (50/200/25)	✓	✓
RPV/FTC/TAF (25/200/25)	✓*	waiver

*Also approved in EU

Low dose pediatric dispersible tablets of TAF for use in children <25kg are under investigation

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The Pediatric ARV Market is Small but Complex

95 adult patients

All ages & weight bands

One pill, once-a-day

5 paediatric patients

Multiple ages and weight bands

Multiple formulations and regimens

Pediatric ARV Formulations

NRTI		
ABC	Tablet (disp,scored) as sulfate	60 mg
ABC	Tablet (scored) as sulfate	60 mg
ABC	Oral liquid as sulfate	100mg/5ml
AZT	Tablet (dispersible, scored)	60 mg
AZT	Oral liquid	50mg/5ml
AZT	Tablet (scored)	60mg
AZT	Capsule	100 mg
AZT	Tablet	100 mg
3TC	Oral liquid	50mg/5ml
3TC	Tablet (dispersible)	30mg
3TC	Tablets	30mg
D4T	Capsule	15mg
D4T	Capsule	20mg
D4T	Powder for Oral solution	5mg/5ml
DDI	Cap, unbuffered, enteric coated	125 mg
DDI	Cap, unbuffered, enteric coated	200 mg
DDI	Tab (buffered, chewable, disp)	25mg
DDI	Tablet (buffered, chewable, dispersible)	50 mg
DDI	Tablet (buffered, chewable, dispersible)	100 mg
DDI	powder for Oral liquid (Buffered)	2g, 4g bottle
FTC	Oral liquid	10 mg/ml
TDF	Oral powder	40mg/scoop
TDF	Tablet (unscored)	150 mg
TDF	Tablet (unscored)	200mg

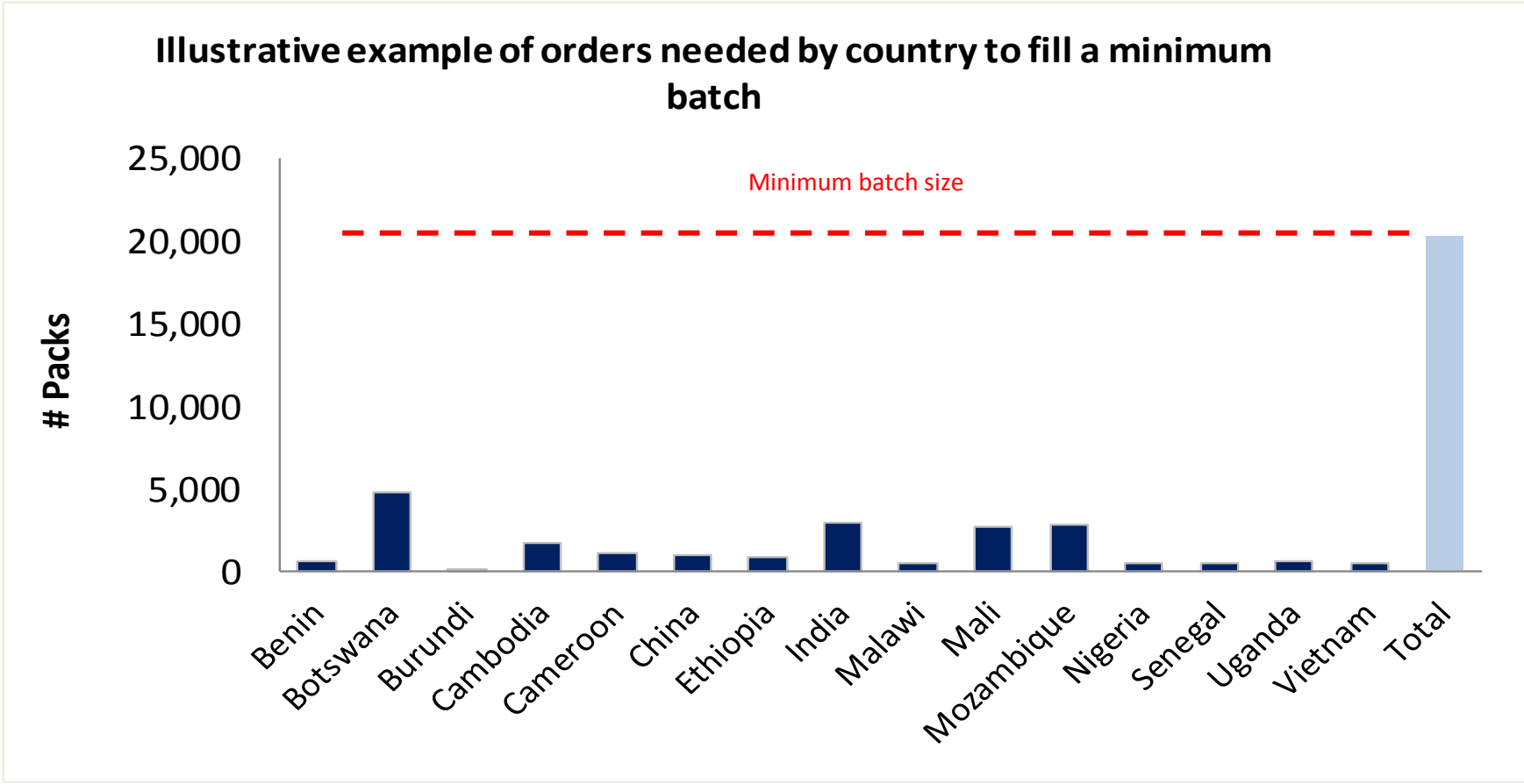
NNRTI		
EFV	Tablet (scored)	200mg
EFV	Tablet	50mg
EFV	Tablet (unscored)	200 mg
EFV	Tablet (disp)	100mg
EFV	Capsules	50 mg
EFV	Capsules	100 mg
EFV	Capsules	200 mg
EFV	Oral liquid	150mg/5ml
NVP	Tablet (dispersible, scored)	50mg
NVP	Tablet (non dispersible)	50mg
NVP	Tablet (non dispersible)	100mg
NVP	Oral liquid	50mg/5ml
NVP	Tablet (dispersible)	100 mg
NVP	Tablet (nondispersible)	20mg
ETV	Tablet	25mg
ETV	Tablet	100mg

PI		
LPV/r	Tablet (hs)	100mg/25mg
LPV/r	Oral liquid	80/ 20 mg/ml
LPV/r	Oral pellets	40mg/10mg/cap
LPV/r	Oral granules	40mg/10mg/packet
RTV	Oral liquid	400mg/5ml
RTV	Oral granules	100mg/packet
RTV	Tablet	25mg 50mg
DRV	Tablets	75 mg
DRV	Tablets	150 mg
DRV	Oral liquid	500mg/5ml
ATV	caps as sulfate	100 mg
ATV	caps as sulfate	150 mg
ATV	Powder	50mg
ATV	caps as sulfate	200 mg
TPV	Oral liquid	500mg/5mL
FPV	Oral liquid	250mg/5mL

Integrase Inhibitors		
RAL	chewable Tabs (scored)	100 mg
RAL	chewable Tabs	25 mg
RAL	Packets for oral susp	100mg
DTG	Film coated tablet	25mg
DTG	Film coated tablet	10mg

FDC's		
AZT/3TC	Tablet (disp scored)	60/30 mg
AZT/3TC	Tablet (scored)	60/30 mg
AZT/3TC/NVP	Tablet (disp scored)	60/30/50 mg
D4T/3TC/NVP	Tablet (disp scored)	6/30/50 mg
D4T/3TC/NVP	Tablet (disp, scored)	12/60/100 mg
D4T/3TC	Tablet (disp, scored)	6/30 mg
D4T/3TC	Tablet (dispersible, scored)	12/30 mg
ABC/3TC	Tablet (disp, scored)	120/60 mg
ABC/3TC	Tablet (scored)	60/30 mg
ABC/3TC/AZT	Tablet (**non** disp, scored)	60/30/60mg
TDF/3TC	Tablet	75mg/75mg

Too many formulation is not a good thing for the generic ARV market



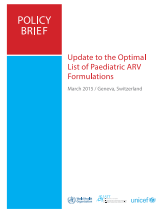
Optimal Paediatric ARV Formulary

- The Optimal Formulary simplifies selection and procurement of paediatric ARV's
  - Normative guidance needed on the best options to deliver all required first- and second- line regimens for paediatric HIV patients
  - Market fragmentation from too many choices leading to instability in the paediatric marketplace
- In 2011 the IATT published the first optimal ARV formulary which has remained a living document
  - Revision in accordance with WHO Guideline
  - Inclusion of new optimal paediatric ARV products
- July 2018: New Optimal Formulary and Limited-use List published alongside new WHO recommendations for pediatric ART

2011

2013

2015



2016

2018

Criteria used for selection of products

Criteria	Description
WHO recommended	Safety and efficacy established
SRA/WHO PQ approved	≥ 1 quality assured product available
User friendly	Easy for HCW's to prescribe Easy for caregivers to administer Supports adherence in children
Optimizes supply chain	Easy to transport Easy to store Easy to distribute
Dosing flexibility	Allows for the widest range of dosing options
Comparative cost	Cost should NOT be the deciding factor in selection of a drug but comparative cost of similar drugs/drug formulations should be considered

Definitions

Optimal Formulary	Minimum number of ARV formulations needed to provide all currently recommended preferred and alternative first and second-line regimens for infants and children, and infant prophylaxis for PMTCT
Limited-use List	ARV Formulations which are included in the WHO guidelines and are needed for a limited time or in low volumes

Adult ARV formulations that may be used in pediatric populations not included

2018 Optimal Formulary: 8 Products

Drug	Formulation	Dose	Discussion/Narrative
AZT	Oral liquid	50mg/5ml, 100ml	For postnatal prophylaxis or neonatal treatment
NVP	Tablet (disp, scored)	50mg	For postnatal prophylaxis
NVP	Oral liquid	50mg/5ml, 100ml	For postnatal prophylaxis or neonatal treatment
LPV/r	Tablet (heat stable)	100mg/25mg	For alternative first-line or second-line for children 10 kg and above and able to swallow tablets whole
LPV/r	Solid oral dosage form	40mg/10mg	For alternative first-line or second-line for children 10 kg and below and not able to swallow tablets whole
AZT/3TC	Tablet (disp, scored)	60mg/30mg	For first-line in special circumstances or second-line in infants and children 4-25 kg
ABC/3TC	Tablet (disp, scored)	120mg/60mg	For preferred first-line or second-line in infants and children
RAL	Chewable scored tablet	25mg	To provide alternative first-line and second-line for infants and children between 3-25 kg

DTG-containing regimens are the preferred first-line treatment for infants and children age 4 weeks-10 years. At the time of this revision, 50mg adult tablets can be used for children weighing 25kg and above. When dosing is confirmed for lower weight bands, the Optimal Formulary and Limited-use List will be reviewed to include paediatric dosage forms of DTG as they are made available.

http://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/

2018 Limited-use List: 10 products

Drug	Formulation	Dose	Discussion/Narrative
LPV/r	Oral liquid	80mg/20mg/ml	For alternative first or second line for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole, until a suitable oral solid dosage form becomes widely available
3TC	Oral liquid	50mg/5ml, 100ml	For neonatal treatment only
ABC	Disp scored tab	60mg	To provide a triple nucleoside regimen in combination with AZT/3TC dual FDC for the duration of TB treatment
DRV	Tablet	75mg	For third-line regimens in children 3 years and above
RTV	Tablet	25mg	For superboosting of LPV/r during TB treatment and boosting of un-coformulated protease inhibitors
RTV	Powder	100mg	For superboosting of LPV/r during TB treatment and boosting of un-coformulated protease inhibitors
ATV	Capsule	200mg	For alternative second-line in combination with RTV 100mg
AZT/3TC/NVP	Disp scored tablet	60mg/30mg/50 mg	For first-line in special circumstances in children below three years until suitable bPI or INSTI dosage forms become widely available
EFV	Scored tablet	200mg	For first-line in special circumstances in children above three years until suitable bPI or INSTI dosage forms become widely available
RAL	Granules for suspension	100mg	For neonatal treatment only

http://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/

Overview

- Background and Rationale for Optimization
- Update on WHO 2019 recommendations for Pediatric ART
- New Pediatric ARV formulations
- The Optimal Formulary and Limited-use List
- **Transition planning**
- Q&A

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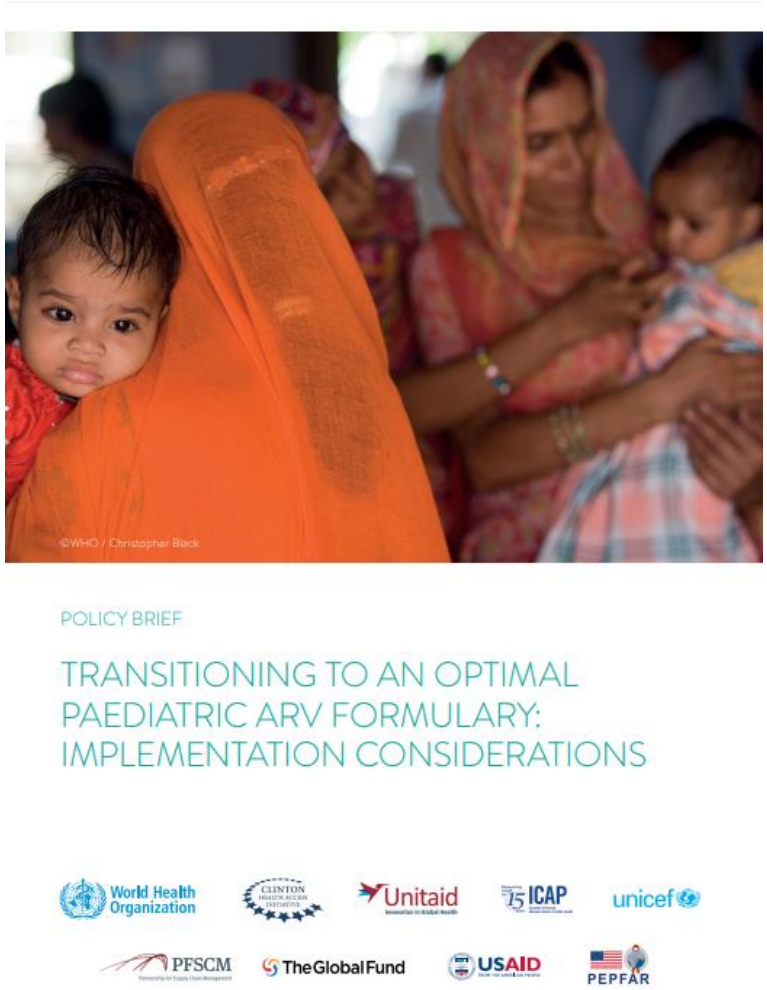
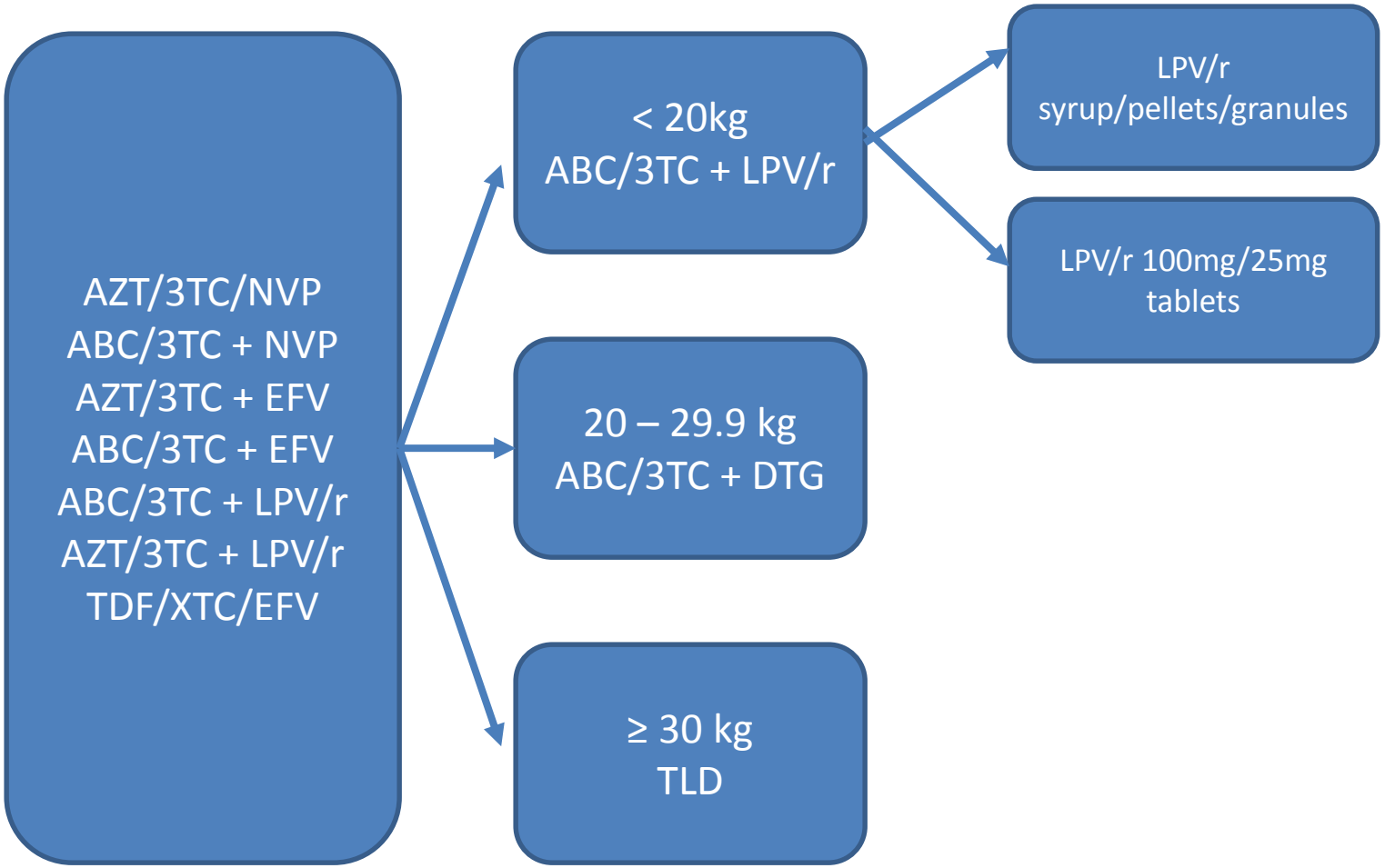
Transitioning to an optimal pediatric ARV formulary: implementation considerations

- **Clinical considerations**
  - Patient eligibility
  - Dosing and administration guidance
  - Transitioning from suboptimal regimens
  - Age appropriate regimen and formulation transition
- **Supply chain and procurement**
  - Quantification
  - Availability
- **Monitoring and Evaluation**
  - Toxicity monitoring and pharmacovigilance



http://apps.who.int/iris/bitstream/handle/10665/273152/WHO-CDS-HIV-18.16-eng.pdf?ua=1

Pediatric ARV Optimization Considerations: 4 Transitions Needed



Developing Transition Guidance

Current regimen	Weight	Optimal regimen for transition	Considerations
AZT/3TC/NVP AZT/3TC/EFV ABC/3TC/NVP	<20 kg	ABC/3TC/LPV/r	Can be transitioned to DTG when they reach 20 kg
	20-30kg	ABC/3TC/DTG	Can be transitioned to TLD when they reach 30 kg
	> 30kg	TLD	Can be maintained through adulthood
ABC/3TC/EFV	<20 kg	No change until reach 20 kg unless treatment failure occurs	Maintain regimen (if stable) to preserve OD dosing until they reach 20kg and can transition to DTG
	20-30kg	ABC/3TC/DTG	Transition to TLD when they reach 30kg
	> 30kg	TLD	Harmonized with adults
ABC/3TC/LPVr AZT/3TC/LPVr	<20 kg	No change until reach 20 kg unless treatment failure occurs	Transition from LPV/r syrup/pellets/granules to tablets as soon as possible. If stable consider transition from AZT/3TC to ABC/3TC 120mg/60mg to reduce pill burden
	20-30kg	ABC/3TC/DTG	If still stable these can be transitioned to TLD when they reach 30 kg
	> 30kg	TLD	Harmonized with adults

	Neonates	Children	Adolescents ≥30kg
Preferred	AZT + 3TC +RAL	ABC + 3TC + DTG	TLD

<u>Considerations for transition</u>

- Viral load availability
- Transitioning of NRTI backbone for those on AZT
- Simplified recommendations
- Clinical Priority
- Use of existing stocks
- Formulations accessible

Peds Pipeline: September 2019 Update*

DTG 50mg and TLD already available

DTG 50mg approved for use in ≥ 20kg
TLD approved for use in ≥ 30kg

Increased capacity for LPV/r pellets/granules → *Supply is less of a constraint*

ABC/3TC/LPV/r "4 in 1"

Anticipated filing → SRA Approval (~ 6 mos) → ~ 6 mos → Availability in country

DTG 5mg disp tablet — All P1093 cohorts (4 wks and up)

Anticipated filing → SRA Approval (~ 6 mos) → ~ 6 mos → Availability in country

DTG 10mg scored tab

Anticipated filing → SRA Approval (~ 6 mos) → ~ 6 mos → Availability in country

*All timelines subject to change

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Thank you!!!

- Increasing NNRTI resistance contributes to low rates of viral load suppression in infants and young children
- New WHO guidance recommends using integrase inhibitors or protease inhibitor-based first line
- New formulations and resources ease ARV administration in young children
- Harmonizing pediatric formularies across countries is essential for supply security

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