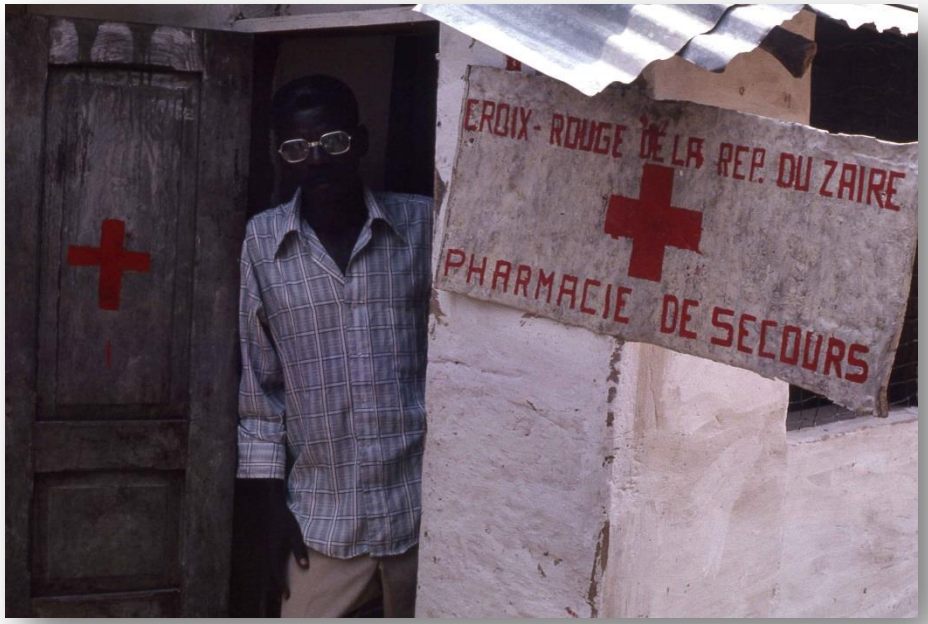
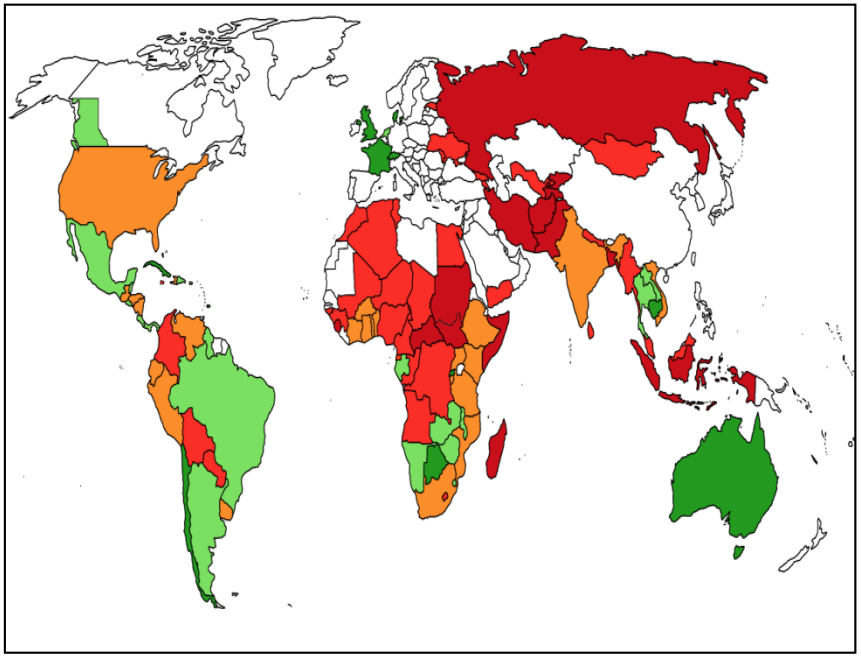
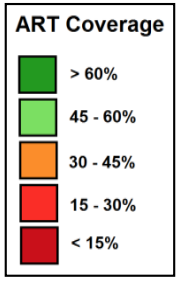
Update on CADO/PADO: what are the challenges in using the current guidelines and foreseen ARV revisions: opportunities and challenges

Treatment and Care Team
Meg Doherty, Marco Vitoria, Martina Penazzato, Nathan Ford

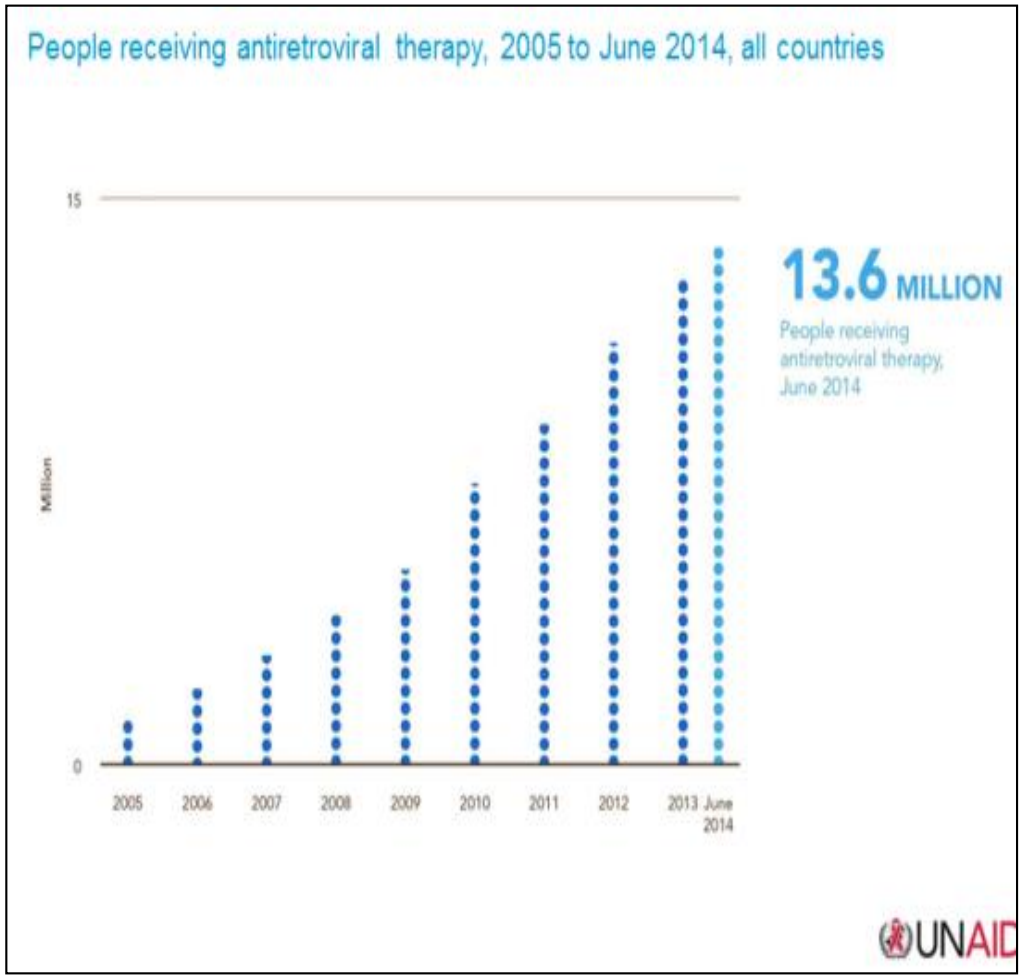


Access to ART worldwide has significantly increased but coverage still very heterogeneous…



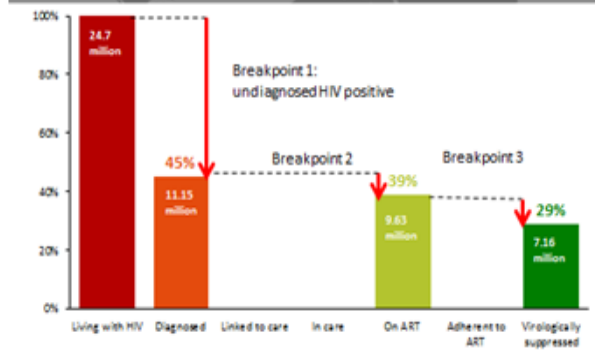


Hill et al. CROI 2015 [abstr 1118]



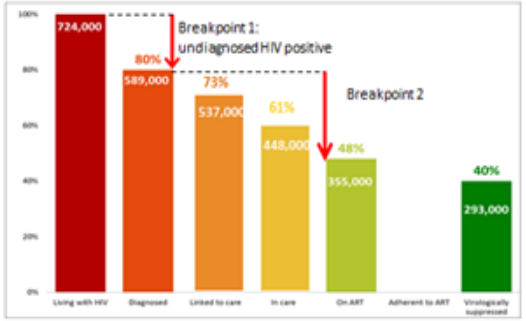
Even in settings with good testing & ART coverage, treatment cascades still show important leakages…

Cascade of HIV care – Sub-Saharan Africa



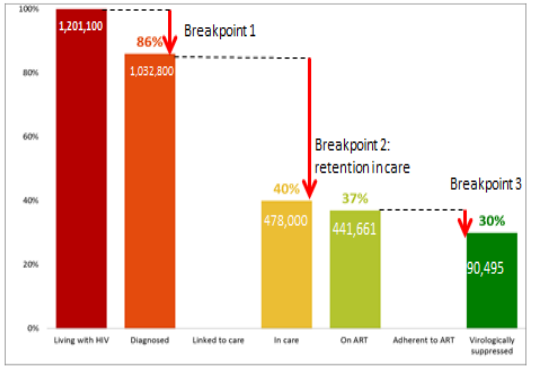
Reference: UNAIDS Gap Report 2014

Cascade of HIV Care – Brazil, 2013



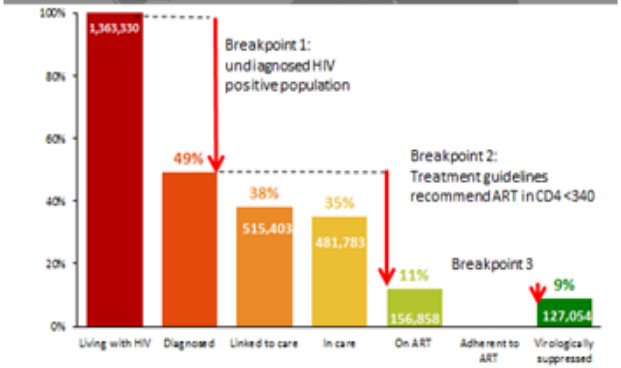
Reference: Brazilian Ministry of Health,Cascade of continuous care in Brazil , 2013. HIV epidemiology report, October 2014, Brazil.

Cascade of HIV care – United States

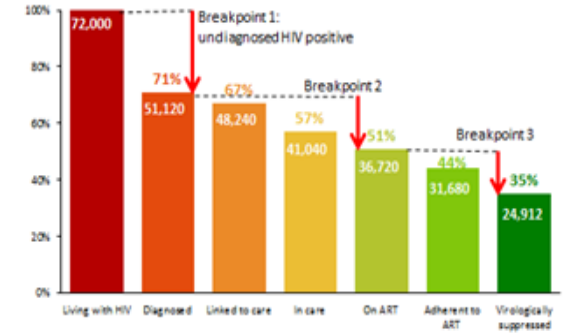


Reference: Heather Bradley, PhD 1, H. Irene Hall, PhD 1, Richard J. Wolitski et al: HIV Diagnosis, Care, and Treatment Among Persons Living with HIV — United States, 2011. November 28, 2014 / 63(47);1113-1117 available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6347a5.htm?s_cid=mm6347a5_w#tab1

Cascade of HIV care – Russia



Cascade of HIV care – British Columbia (CA)



Reference:Nosyk B, Montaner JS, Colley G, Lima VD, Chan K, Heath K, Yip B, Samji H, Gilbert M, Barrios R, Gustafson R, Hogg RS, STOP HIV/AIDS Study Group. The cascade of HIV care in British Columbia, Canada, 1996-2011: a population-based retrospective cohort study. The Lancet Infectious diseases 2014(1) 40-49.

Hill et al. CROI 2015 [abstr 1118]

World Health Organization

HIV TREATMENT

Major WHO Normative Documents on HIV Treatment, Care and Prevention (2013-2014)

HIV/AIDS Department

2013

2014

2015

2013 Consolidated WHO ART Guidelines

Use of devices for adult MC for HIV prevention

Skin & Oral Manifestations in PLHIV

March 2014 Guidelines Supplement

Consolidated guidelines for key populations

December 2014 Guidelines Supplement

Technical update on VL testing implementation

QA for PoCT handbook

2013 Global Update on HIV Treatment

Guidance for HIV HTC & Care for Adolescents

2013-2016 ARV forecast & drug price database

Screening, care and Treatment of Hepatitis C infection

Technical report on access to ARVs in LMIC

Technical report on use and availability of HIV diagnostics

2014 Update Report on Health Sector Response to HIV

World Health Organization

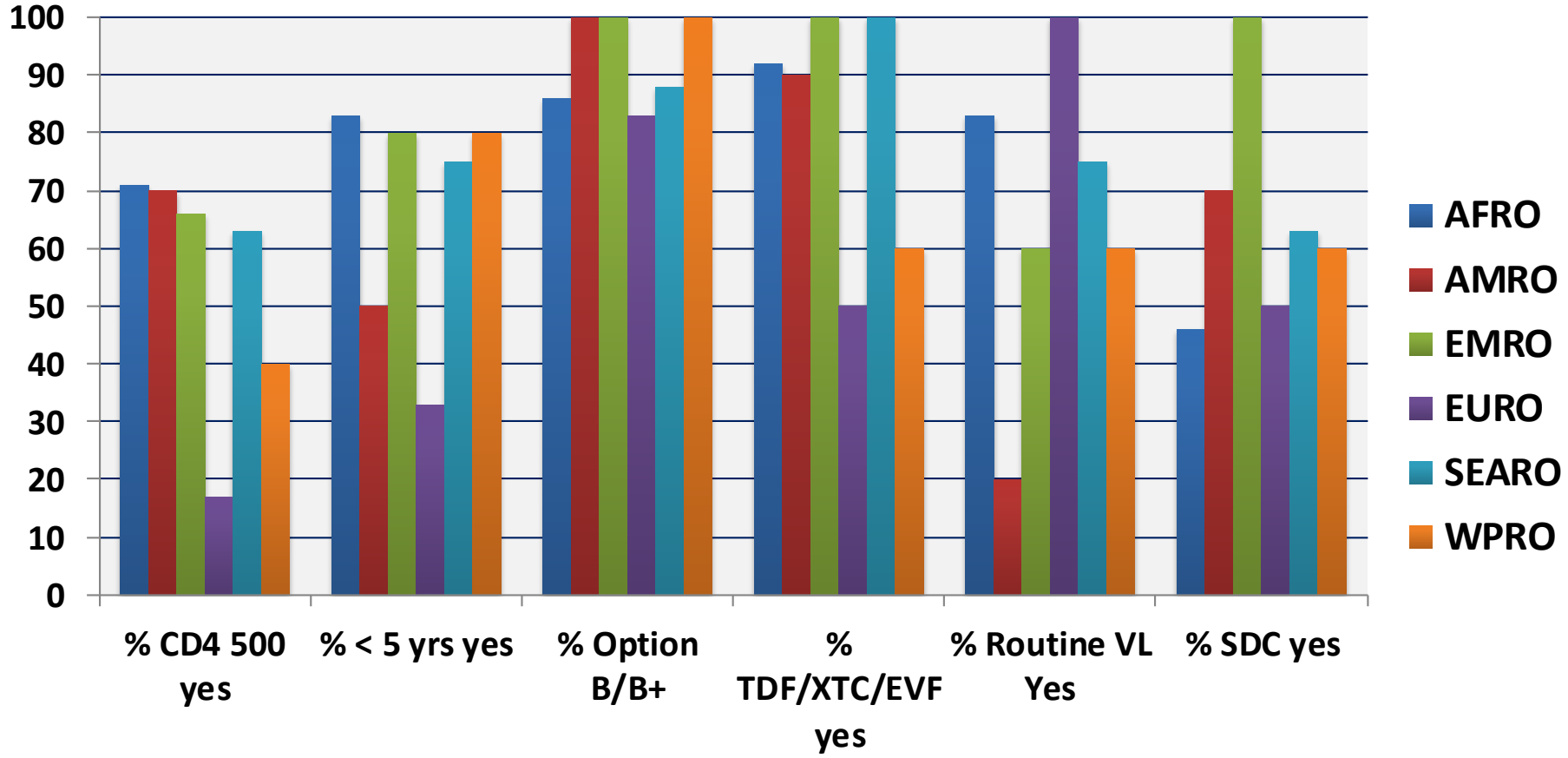
World Health Organization

WHO, Feb 2015

Making Impact in Countries – 2013-14 ARV Policies

(% responding yes, by region)

Policy uptake in 58 WHO focus countries end 2014, by region



World Health Organization

Uptake of 2013 recommendations as of Oct 2014

HIV TREATMENT

Drug Optimization: an ongoing process

Think Tank Meeting

ART sequencing meeting

Priorities for ART Optimization

Conference on Drug optimization (CADO-1)

Conference on Drug optimization 2 (CADO-2)

Paediatric Conference on ARV Drug optimization 1 (PADO-1)

Paediatric Conference on ARV Drug optimization 2 (PADO-2)

Conference on Drug optimization 3 (CADO-3)

Paediatric Conference on ARV Drug optimization 3 (PADO-3)

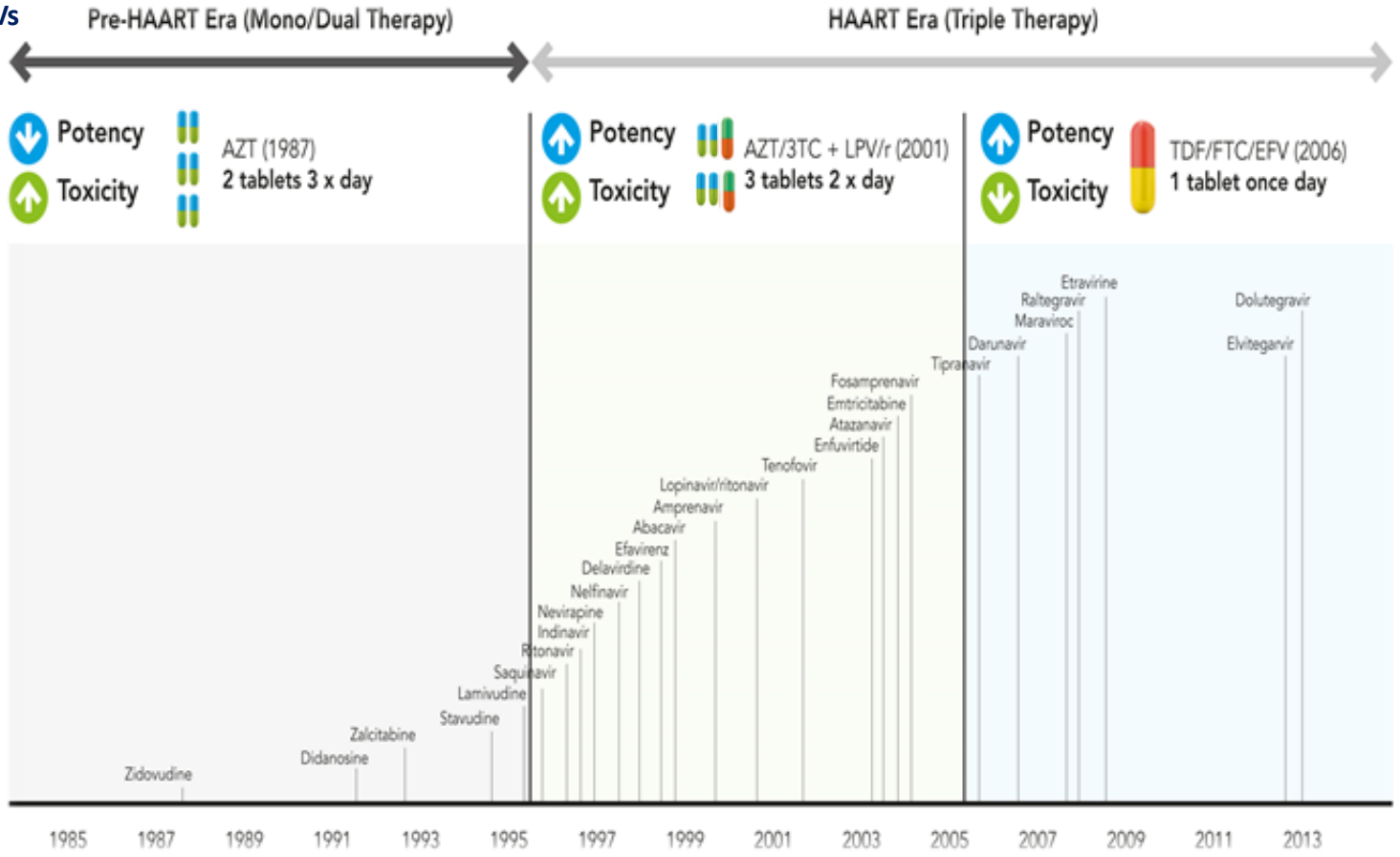
2011 2012 2013 2014 2015 2016

World Health Organization

Temporal evolution of ARV drug pipeline: moving towards smarter and better HIV treatment options

Target Product Profile for ARVs

- Tolerability
- Resistance
- Convenience
- Special populations
- Cost



CADO 2 Report, 2013

World Health Organization

HIV TREATMENT

Key messages from WHO guidelines on ARV optimization

1. Once daily regimens are better than twice-daily regimens (clinical and programmatic).

2. FDCs are preferred for simplification, convenience, adherence, more efficient procurement, lower risk of stock outs and resistance.

3. EFV is superior to NVP in the long term(clinical and programmatic).

4. For sequencing, TDF use has advantages over other NRTIs (clinical and programmatic).

Adapted from Poly Clayden (i-Base/TAG Pipeline Report, 2014)

World Health Organization

What is the ideal ARV regimen for public health approach?

1. Safe and effective

2. No need to adjust doses for:

   - Malnourished people
   - Pregnant women
   - TB treatment
   - Harmonization with paediatrics

3. Affordable in a wide range of countries (patents)

Target Product Profile for ARVs

CADO 2 Report, 2013

Future options for first-line treatments?

TDF/3TC/EFV is still the main WHO recommended first-line treatment

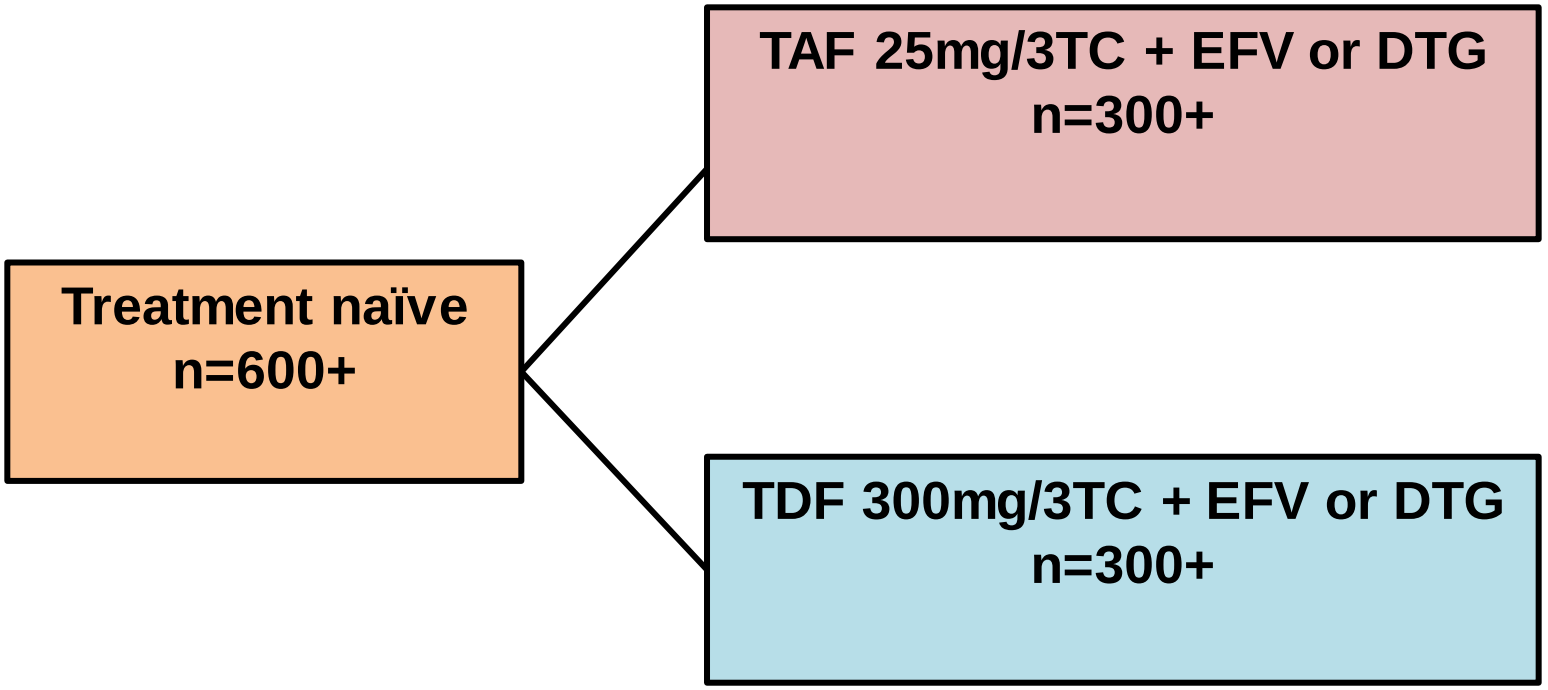
Are there alternatives for the future?

- TDF/3TC/EFV400 ?
- TDF/FTC/DTG ?
- TAF/3TC/DTG ?
- TAF/FTC/RPV
- Other regimens?

Dose-optimization trials to improve safety

ARV (Trial)	Main adverse event	Current dose (mg)	Optimised dose (mg)
EFV (ENCORE)	**CNS**	**600 OD**	**400 OD**
ATV/r (LASA)	Renal stones, bilirubin	300/100 OD	200/100 OD
TDF + PI (pK)	**Renal/ bone**	**300 OD**	**200 OD (+PI)**
DRV/r (FR/IT/ES)	**Lipids/ GI / renal**	**800/100 OD**	**400/100 OD**
D4T (Africa)	Neuropathy/ lipoatrophy	30 BID	20 BID

TDF vs TAF in use of EFV or DTG – new study needed



- Double-blinded, randomised
- Primary endpoints: HIV RNA <50 copies/mL (FDA Snapshot)
- Secondary endpoints: serum creatinine, bone density (hip/spine)

Drug interactions – what is known?

PK effects	Food	Pregnancy	TB
EFV 600mg	Small effect	Small effect	Short-term effect
EFV 400mg	No data	No data	No data
Dolutegravir	Metal ions ↓	No data	No data
Rilpivirine	Fasting ↓	No data	No data

Prices of FDCs versus generics in 2017, in middle or high income countries?

Single tablets
$7,000 - $10,000/year

TDF/FTC/EFV
TDF/FTC/RPV
TDF/FTC/EVG/COBI
ABC/3TC/DTG

Three separate tablets
< $1000/year

Generic TDF

Generic 3TC

Generic EFV or PI/r

Sources: BNF 2014, generic company prices

Patent expiry dates of major ARV drugs/combinations: 2015-2029

11 years (2015-2026) when many drugs are available as individual generics, but co-formulated versions are still on-patent

2015: ZDV, 3TC, NVP, EFV, RTV – already available as generics

2016: ABC, LPV/r

2017: TDF, ATV/r, DRV/r

2019: ABC/3TC

2021: ETR

2024: TDF/FTC

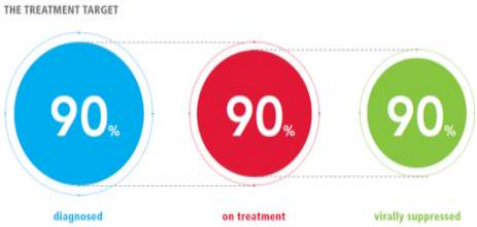
2025: RALTEGRAVIR

2026: TDF/3TC/EFV, TDF/FTC/RPV

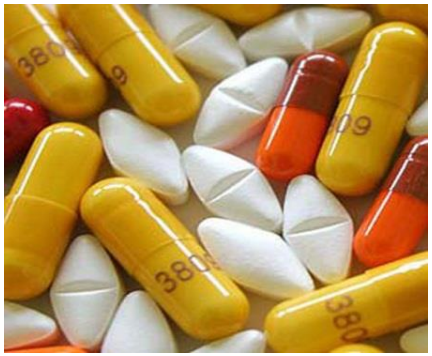
2029: ABC/3TC/DTG , TAF/FTC/EVG/COBI

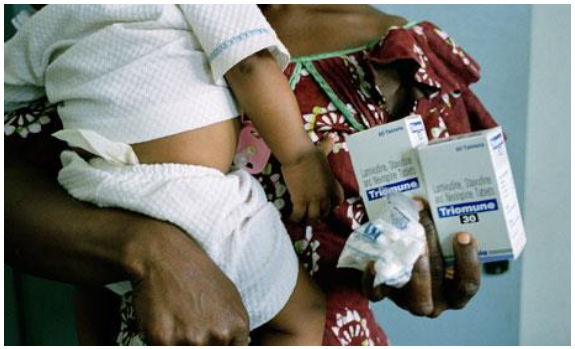
Ref: MSF2014: Untangling the web of ARV price reductions

Summary: What WHO Expected Innovations in Treatment & Drugs ?



- Low dose of strategic drugs (EFV, TDF, PIs)
- FDCs for 2nd and 3rd line
- Pellets and 4 in 1 FDCs for children
- Integrase inhibitors for both 1st and 2nd line
- DRV as a boosted FDC





Perspectives in ART Optimization Agenda

Summary Table

ART Optimization Strategy	Tolerability	Resistance	Convenience	PW, TB, children	Cost Reduction	What action are needed?	Estimated Timeline
Low dose EFV	✓	?	✓	?	✓	• pK studies (PW & TB)	1-2 yrs
Low dose DRV/r (as FDC)	✓	?	✓	?	✓	• pK studies (DRV:RTV ratio) • RCT (standard vs low dose)	1-2 yrs
Use of DTG (as FDC)	✓	✓	✓	?	✓	• Studies in PW, TB & children • Comparative trials • RCT (DRV/r + DTG in 2nd line)	2-5 yrs
Use of TAF	✓	?	✓	?	✓	• Comparative trials using DTG • Studies in PW, TB & children	2-5 yrs
Long-acting formulations	✓	?	✓	✓	✓	• Phase II/III studies (treatment & preventive trials)	> 5 yrs

HIV TREATMENT

Updates from PADO 2 and lead up to the next WHO guidelines

World Health Organization

Optimizing use of ARVs

Developing tools for implementation targeted to HCW (ie drug information pages) or to programme managers (IATT formulary)

Developing weight-based dosing of existing drugs such as TDF and DRV/r or recommending optimal dosing and ratios for FDC to be developed

Weight-band dosing

Guiding Drug development

Developing tools

Estimating the ARV need and setting mid-long term priorities for new formulations and new drugs and defining TPP

World Health Organization

Setting priorities

- Mid-term priorities
  - More potent drugs for second line in young children
  - DRV/r or RAL as the 3rd line options
- Long-term priorities
  - INT in 1st line as opportunity for full harmonization
  - NNRTI left for 3rd line combinations

		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			

Roadmap to meet treatment targets

- Accurate forecasting of demand for paediatric ARVs
- Approval of new drugs and new formulations
- Patent-sharing agreement for key drugs and diagnostics

- Innovative financial mechanisms to sustain a diminishing market

PADO1

Established priorities for new drugs and formulation development

Outlined a roadmap to streamline access and uptake of optimal products

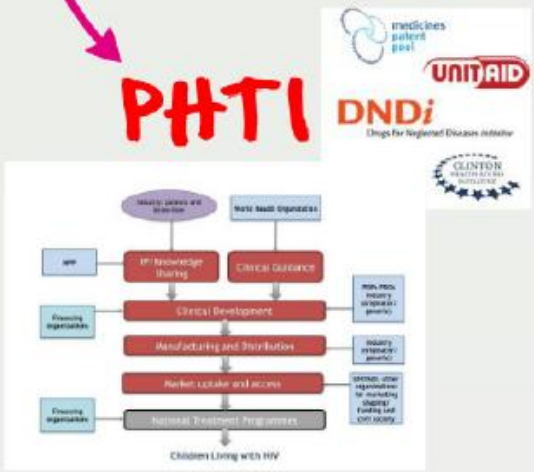
Leveraging existing mechanisms of collaboration

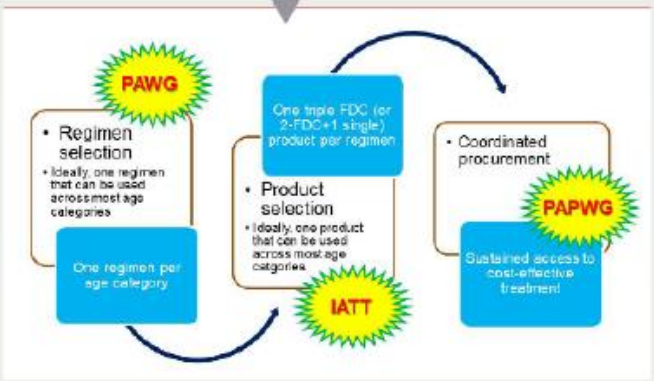
PADO	• New drugs, mid- and long-term priorities • New formulations
WHO Guidelines	• Existing drugs • Existing formulations
PAWG	• Critical technical enabler for formulation development and dose ratios
IATT Formulary	• Optimized formulations for procurement • Minimum number of products to build regimens recommended by guidelines
PAPWG	• Coordinated procurement of paediatric ARVs

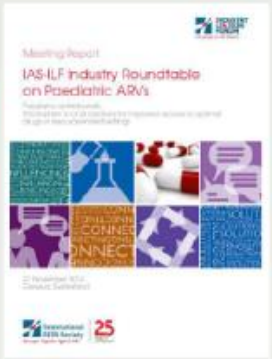
Adapted from: ILF/CIPHER Thematic Roundtable on Paediatric HIV, 2014

New energies, New coordination, New collaboration

- Open conversation with manufacturers
- More dynamic interaction with regulators
- New vision and new platforms to speed up R&D
- Productive interaction between procurement agencies and different stakeholder supporting implementation in countries







“Paediatic week” - Drug optimization

OPTIMIZING HIV TREATMENT OPTIONS AND IDENTIFYING PRIORITY MEDICINES FOR CHILDREN

Meeting on paediatric ARV drug optimization - PADO 2, 8-9 December

Building upon the progress made after PADO 1 meeting, held in Dakar in 2013, WHO is convening a second meeting (PADO 2) to further advance optimization in paediatric ART, and to develop inputs for the WHO 2015 consolidated ARV guidelines' process. Participants will also establish priorities for drug and formulation development and identify research gaps on the use of ARVs for infants, children and adolescents. Open to members and invitees. Contact: Martina Penazzato, WHO

DEVELOPING PRIORITY MEDICINES FOR CHILDREN

Meeting of the Paediatric HIV Treatment Initiative - PHTI, 10 December

The PHTI aims to accelerate the development of paediatric formulations as recommended by WHO. One of the priority formulations is a paediatric-adapted formulation of ABC/3TC/EFV, needed for first-line treatment of children between 3 and 10 years of age. This meeting will convene paediatricians, researchers, pharmacologists, formulation experts, drug regulators and companies to discuss issues related to the development of this product. Open to members and invitees only. Contact: Fernando Pascual, MPP

OPTIMIZING SELECTION AND PROCUREMENT OF EXISTING PAEDIATRIC PRODUCTS

Inter-Agency Task Team (IATT) formulary revision meeting, 10 December

The Optimal Formulary List of paediatric ARV formulations jointly published by IATT, WHO and UNICEF provides guidance to funders, implementing partners, procurement agencies and countries to enable a consolidated demand for optimal products and to ensure a sustainable supply of medicines for children living with HIV. This meeting will focus on updates required for the optimal list, and on activities needed to support the use of the list, including for the WHO's 2015 consolidated ARV guidelines' development process. Open to members and invitees. Contacts: Nandita Sugandhi,CHAI and David Jamieson, SCMS

ENABLING EFFECTIVE PROCUREMENT AND SUPPLY OF EXISTING PAEDIATRIC PRODUCTS

Meeting of the PAEDIATRIC ARV PROCUREMENT WORKING GROUP, 11 December

The Paediatric ARV Procurement Working Group (PAPWG) was established to adopt a coordinated approach to the procurement of paediatric ARVs to secure the paediatric ARV market and to support sustained treatment scale-up. The Global Fund is convening this meeting with partners to share updates as well as to define priorities in innovation and expected outcomes. Open to invitees and members. Contacts: Martin Auton, the Global Fund and Gitanjali Sakhuja, UNICEF

World Health Organization

medicines patent pool

UNITAID

DNDi Drugs for Neglected Diseases *initiative*

CLINTON HEALTH ACCESS INITIATIVE

IATT THE INTERAGENCY TASK TEAM
The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

unicef

The Global Fund

Elizabeth Glaser Pediatric AIDS Foundation

International AIDS Society Stronger Together Against HIV

Médecins Sans Frontières

CLINTON HEALTH ACCESS INITIATIVE

KEMSA

ECS

Pan American Health Organization

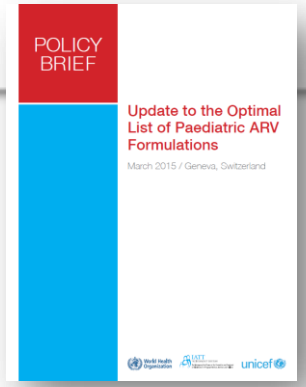
PFSCM SCMS

2015 Optimal Paediatric ARV Formulary

Drug Class	Drug	Dosage Form	Strength
NNRTI	**EFV**	Tablet (scored)	200 mg
NNRTI	**NVP**	Tablet (disp, scored)	50 mg
NNRTI	**NVP**	Oral liquid*	50 mg / 5mL, 100ml
PI	**LPV/r**	Tablet (heat stable)	100 mg / 25mg
PI	**LPV/r**	Oral liquid	80 mg / 20 mg/ml
FDC	**AZT/3TC**	Tablet (disp, scored)	60 mg / 30 mg
FDC	**AZT/3TC/NVP**	Tablet (disp, scored)	60 mg / 30 mg / 50 mg
FDC	**ABC/3TC**	Tablet (disp, scored)	60 mg / 30 mg, 120mg / 60mg

** For infant prophylaxis during PMTCT*

IATT
THE INTERAGENCY TASK TEAM
The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children



PADO2 Advice to the WHO 2015 Guidelines development

- **Adolescents:**
  - Maximising efficacy and adherence while preserving harmonization.
  - Desire to have more effective and forgiving regimen but harmonization should be prioritized.
  - More information is needed on of low dose EFV for 1st line.
- **Young children:**
  - lack of appropriate formulations and dosing guidance remain key barriers for newborns and young children
- **Second and third line:**
  - Integrase inhibitors particularly recommended for children failing treatment after starting a PI-based regimens.
  - Once-a-day regimens in FDCs when possible

PADO 2 Priorities for Formulations development

Formulation	Next steps
ABC or AZT+3TC+LPV/r (4 in 1)	Under development (DNDi)
ABC/3TC/EFV	Ratio and dosing schedule are being finalized (PAWG)
RAL for infants	Determine appropriate WHO weight band dosing (PAWG)
Dispersible NVP 20mg	Provide guidance to product selection and drug procurement (IATT)
DRV/r and ATV/r	To be developed (PHTI)
DTG/XTC/TAF	Advocate for development of full PIP for single strength TAF (PAWG)
DTG	WHO weight band dosing to be reviewed (PAWG)

PADO 2 Priorities for Drug development

	0-3 yrs	3-10 yrs	10 yrs +
FIRST LINE			
Mid-term (5 yr)	ABC/3TC/DTG		TAF/3TC/DTG
Long term (10 yr)	TAF/3TC/DTG		
SECOND LINE			
Mid-term (5 yr)	AZT/3TC/RAL or LPV/r	AZT/3TC/DRV/r	TAF/3TC/DRV/r
Long term (10 yr)	AZT/3TC/LPV/r	RPV/DRV/r or AZT/3TC/DRVr	

- Full **harmonization** will only be possible if drug development for adults and children is aligned while considering appropriate specificities.
- **Methodological** approaches should be critically considered to explore opportunities for faster R&D for children and adolescents

How much harmonization do we need?

Care taker

- Same regimen for all family members may be helpful
- Avoid inappropriate drug sharing

Health care Provider

- More familiar with adult regimens
- But different formulations still need to be available
- Dosing changes still necessary as child grows/ages

Programme /supply manager

- Streamline procurement
- Simplify forecasting and ordering

Manufacturers

- Ensure API availability
- Lower cost of production

Harmonization is critical but when formulations are different benefits of harmonization are potentially limited

Development of **scored dispersible adults tablets** becomes essential

PADO2 Research gaps

- Safety and efficacy of ARVs in newborns
- Adolescent-specific acceptability and toxicity
- Value of performing genotyping after 2nd treatment failure in children
- PK of ATV, DRV, and DTG in TB co-treatment; DTG with ABC/3TC.
- DTG for children less than 12 years particularly in combination with TAF; TAF < 6 unboosted
- Documentation of clinical and operational barriers to switching regimen

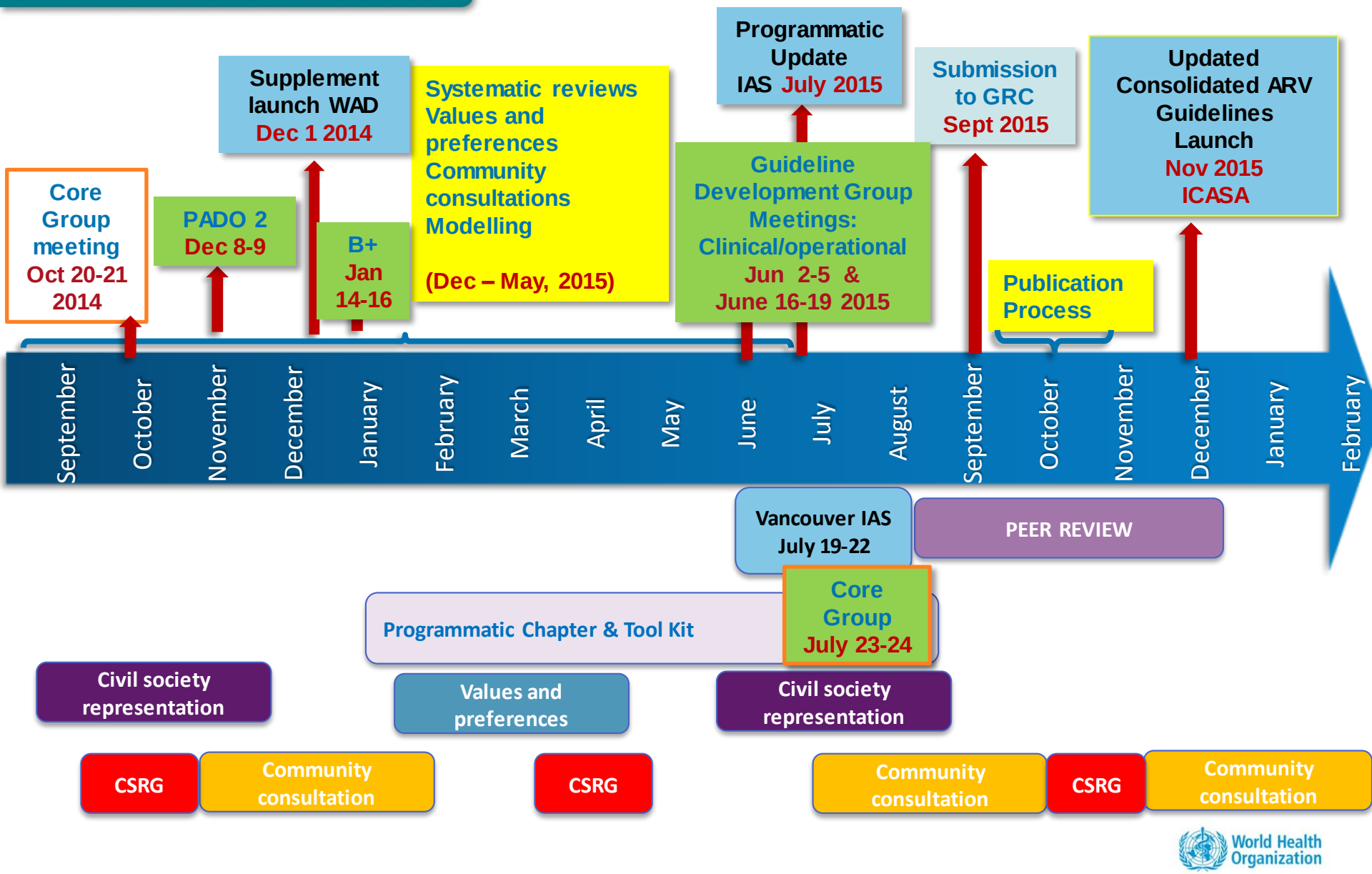
Next Steps CADO / PADO

1. Dissemination to manufacturers
2. Development summary manuscript on adult think tank
3. PAWG to endorse paediatric weight band dosing for RAL, DTG
4. Inform the decision-making process for the 2015 WHO consolidated Guidelines
5. Review EOI based on CADO Think Tanks & PADO2 outcomes
6. EML revision to capture potential changes in ARV guidelines and IATT optimal formulary revision

STRATEGIC USE OF ANTIRETROVIRALS

WHO 2015 Guidelines: Timelines

HIV/AIDS Department



World Health Organization